UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE NEW ENGLAND COMPOUNDING PHARMACY, INC. PRODUCTS LIABILITY LITIGATION	MDL No. 2419 Dkt. No. 1:13-md-2419 (RWZ)
THIS DOCUMENT RELATES TO: All Actions	

DECLARATION OF THOMAS M. SOBOL IN SUPPORT OF THE PLAINTIFFS' STEERING COMMITTEE'S OPPOSITION TO LIBERTY INDUSTRIES, INC.'S OMNIBUS MOTION FOR SUMMARY JUDGMENT IN CASES FILED BY PLAINTIFFS INJECTED IN INDIANA

I, Thomas M. Sobol, declare as follows:

1. I am a partner in the Boston office of the law firm Hagens Berman Sobol Shapiro LLP, and Lead Counsel in the *In re New England Compounding Pharmacy, Inc. Products Liability Litigation*, MDL No. 2419, Civil Action No. 1:13-md-2419-FDS, in the United States District Court for the District of Massachusetts.

2. I submit this declaration in support of the Plaintiffs' Steering Committee's Opposition to Liberty Industries, Inc.'s Omnibus Motion for Summary Judgment in Cases Filed by Plaintiffs Injected in Indiana.

3. Attached hereto are true and accurate copies of the following documents that have been provided by the parties in the course of both formal and informal discovery in this case:

a. Exhibit 1: ISO 14644-1:2001(E): Cleanrooms and associated controlled environments;

b. Exhibit 2: ISO 14644-4:2001(E): Cleanrooms and associated controlled environments;

c. Exhibit 3: Email string ending on Friday, March 14, 2008, 11:07 AM;

d. Exhibit 4: Email dated Friday, September 2, 2005, 7:22 AM;

e. Exhibit 5: Letter from Doug Hall of Liberty to Greg Conigliaro of NECC dated November 21, 2005;

f. Exhibit 6: Document titled "NECC #2 – Percentage of Completion & Schedule of Construction," dated March 21, 2006;

g. Exhibit 7: Document titled "NECC #2 – Percentage of Completion & Schedule of Construction," dated April 5, 2006;

h. Exhibit 8: Document titled "Internal Memo" to GAP and RCK from JCE dated May 10, 2006;

i. Exhibit 9: Email dated Monday, July 10, 2006, 10:56 AM;

j. Exhibit 10: Document titled "New England Compounding Center – Ameridose Cleanroom" dated July 12, 2006;

k. Exhibit 11: ENV Services Certificate of Compliance for Ameridose, Framingham, MA 01702 Cleanroom;

l. Exhibit 12: Memorandum document to GAP and RCK from JCE dated August 17, 2006;

m. Exhibit 13: Liberty "Job Completion Sign-Off Sheet," dated August 11, 2006;

n. Exhibit 14: Transcript excerpts of the deposition of Jeffrey C. Erickson dated November 18, 2014;

o. Exhibit 15: NECC Cleanroom compounding sites (NECC_USMA001102100-06); and

p. Exhibit 16: Declaration of Dr. Philip J. Austin, Ph.D.

Declared under the penalties and pains of perjury.

December 22, 2014

/s/ Thomas M. Sobol
Thomas M. Sobol

EXHIBIT 1

INTERNATIONAL STANDARD

ISO 14644-1

First edition
1999-05-01

Cleanrooms and associated controlled environments —

Part 1:
Classification of air cleanliness

Salles propres et environnements maîtrisés apparentés —

Partie 1: Classification de la propreté de l'air

American National Standard
ANSI/IEST/ISO 14644-1

Reference number
ISO 14644-1:1999(E)

Contents

To order a copy in the United States, contact ISO Member Body:
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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and nongovernmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75% of the member bodies casting a vote.

International Standard ISO 14644-1 was prepared by Technical Committee ISO/TC 209, *Cleanrooms and associated controlled environments.*

ISO 14644 consists of the following parts, under the general title *Cleanrooms and associated controlled environments*:

— *Part 1: Classification of air cleanliness*

— *Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1*

— *Part 3: Metrology and test methods*

— *Part 4: Design, construction and start-up*

— *Part 5: Operations*

— *Part 6: Terms and definitions*

— *Part 7: Enhanced clean devices*

Users should note that the titles listed for parts 2 to 7 are working titles at the time of the release of part 1. In the event that one or more of these parts are deleted from the work programme, the remaining parts may be renumbered.

Annexes B and C form an integral part of this part of ISO 14644. Annexes A, D, E, and F are for information only.

Introduction

Cleanrooms and associated controlled environments provide for the control of airborne particulate contamination to levels appropriate for accomplishing contamination-sensitive activities. Products and processes that benefit from the control of airborne contamination include those in such industries as aerospace, microelectronics, pharmaceuticals, medical devices, food, and healthcare.

This part of ISO 14644 assigns ISO classification levels to be used for the specification of air cleanliness in cleanrooms and associated controlled environments. It also prescribes the standard method of testing as well as the procedure for determining the concentration of airborne particles.

For classification purposes, this part of ISO 14644 is limited to a designated range of considered particle sizes for determination of particle concentration limits. This part of ISO 14644 also provides standard protocols for the determination and designation of cleanliness levels that are based on airborne concentrations of particles smaller or larger than the size range designated for classification.

This part of ISO 14644 is one of a series of standards concerned with cleanrooms and contamination control. Many factors besides airborne particulate cleanliness must be considered in the design, specification, operation, and control of cleanrooms and other controlled environments. These are covered in some detail in other parts of the International Standards prepared by ISO/TC 209.

In some circumstances, relevant regulatory agencies may impose supplementary policies or restrictions. In such situations, appropriate adaptations of the standard testing procedures may be required.

Cleanrooms and associated controlled environments —

Part 1: Classification of air cleanliness

1 Scope

This part of ISO 14644 covers the classification of air cleanliness in cleanrooms and associated controlled environments exclusively in terms of concentration of airborne particles. Only particle populations having cumulative distributions based on threshold (lower limit) sizes ranging from 0,1 µm to 5 µm are considered for classification purposes.

This part of ISO 14644 does not provide for classification of particle populations that are outside of the specified particle size range, 0,1 µm to 5 µm. Concentrations of ultrafine particles (particles smaller than 0,1 µm) and macroparticles (particles larger than 5 µm) may be used to quantify these populations in terms of U descriptors and M descriptors, respectively.

This part of ISO 14644 cannot be used to characterize the physical, chemical, radiological, or viable nature of airborne particles.

NOTE The actual distribution of particle concentrations within incremental size ranges normally is not predictable and typically is variable over time.

2 Definitions

For the purposes of this part of ISO 14644, the following definitions apply.

2.1 General

2.1.1

cleanroom
room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary

2.1.2

clean zone
dedicated space in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the zone, and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary

NOTE This zone may be open or enclosed and may or may not be located within a cleanroom.

2.1.3

installation
cleanroom or one or more clean zones, together with all associated structures, air-treatment systems, services, and utilities

2.1.4

classification
level (or the process of specifying or determining the level) of airborne particulate cleanliness applicable to a cleanroom or clean zone, expressed in terms of an ISO Class *N*, which represents maximum allowable concentrations (in particles per cubic metre of air) for considered sizes of particles

NOTE 1 The concentrations are determined by using equation (1) in 3.2.

NOTE 2 Classification in accordance with this International Standard is limited to the range extending from ISO Class 1 through ISO Class 9.

NOTE 3 The considered particle sizes (lower threshold values) applicable for classification in accordance with this International

Standard are limited to the range from 0,1 µm through 5 µm. Air cleanliness may be described and specified (but not classified) in terms of U descriptors or M descriptors (see 2.3.1 or 2.3.2) for considered threshold particle sizes that are outside of the range covered by classification.

NOTE 4 Intermediate ISO classification numbers may be specified, with 0,1 the smallest permitted increment; i.e., the range of intermediate ISO classes extends from ISO Class 1,1 through ISO Class 8,9.

NOTE 5 Classification may be specified or accomplished in any of three occupancy states (see 2.4).

2.2 Airborne particles

2.2.1

particle
solid or liquid object which, for purposes of classification of air cleanliness, falls within a cumulative distribution that is based upon a threshold (lower limit) size in the range from 0,1 µm to 5 µm

2.2.2

particle size
diameter of a sphere that produces a response, by a given particle-sizing instrument, that is equivalent to the response produced by the particle being measured

NOTE For discrete-particle-counting, light-scattering instruments, the equivalent optical diameter is used.

2.2.3

particle concentration
number of individual particles per unit volume of air

2.2.4

particle size distribution
cumulative distribution of particle concentration as a function of particle size

2.2.5

ultrafine particle
particle with an equivalent diameter less than 0,1 µm

2.2.6

macroparticle
particle with an equivalent diameter greater than 5 µm

2.2.7

fibre
particle having an aspect (length-to-width) ratio of 10 or more

2.3 Descriptors

2.3.1

U descriptor
measured or specified concentration, of particles per cubic metre of air, including the ultrafine particles

NOTE The U descriptor may be regarded as an upper limit for the averages at sampling locations (or as an upper confidence limit, depending upon the number of sampling locations used to characterize the cleanroom or clean zone). U descriptors cannot be used to define airborne particulate cleanliness classes, but they may be quoted independently or in conjunction with airborne particulate cleanliness classes.

2.3.2

M descriptor
measured or specified concentration of macroparticles per cubic metre of air, expressed in terms of the equivalent diameter that is characteristic of the measurement method used

NOTE The M descriptor may be regarded as an upper limit for the averages at sampling locations (or as an upper confidence limit, depending upon the number of sampling locations used to characterize the cleanroom or clean zone). M descriptors cannot be used to define airborne particulate cleanliness classes, but they may be quoted independently or in conjunction with airborne particulate cleanliness classes.

2.4 Occupancy states

2.4.1

as-built
condition where the installation is complete with all services connected and functioning but with no production equipment, materials, or personnel present

2.4.2

at-rest
condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present

2.4.3

operational
condition where the installation is functioning in the specified manner, with the specified number of personnel present and working in the manner agreed upon

Table 1 — Selected airborne particulate cleanliness classes for cleanrooms and clean zones

ISO classification number (*N*)	Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with equation (1) in 3.2)					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1 000	237	102	35	8	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000
NOTE Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level						

2.5 Roles

2.5.1

customer
organization, or the agent thereof, responsible for specifying the requirements of a cleanroom or clean zone

2.5.2

supplier
organization engaged to satisfy the specified requirements of a cleanroom or clean zone

3 Classification

3.1 Occupancy state(s)

The particulate cleanliness of air in a cleanroom or clean zone shall be defined in one or more of three occupancy states, viz. "as-built", "at-rest", or "operational" (see 2.4).

NOTE It should be recognized that the "as-built" state is applicable to newly completed or newly modified cleanrooms or clean zones. Once testing in the "as-built" state is completed, further testing for compliance will be performed in the "at-rest" or the "operational" state, or both.

3.2 Classification number

Airborne particulate cleanliness shall be designated by a classification number, *N*. The maximum permitted concentration of particles, C_n, for each considered particle size, *D*, is determined from the equation:

$$C_n = 10^N \times \left(\frac{0,1}{D}\right)^{2,08} \quad (1)$$

where

C_n is the maximum permitted concentration (in particles per cubic metre of air) of airborne particles that are equal to or larger than the considered particle size. C_n is rounded to the nearest whole number, using no more than three significant figures.

N is the ISO classification number, which shall not exceed a value of 9. Intermediate ISO classification numbers may be specified, with 0,1 the smallest permitted increment of *N*.

D is the considered particle size, in micrometres.

0,1 is a constant, with a dimension of micrometres.

Table 1 presents selected airborne particulate cleanliness classes and the corresponding particle concentrations for particles equal to and larger than the considered sizes shown. Figure A.1 (see annex A) provides a representation of the

selected classes in graphical form. In case of dispute, the concentration C_n as derived from equation (1) shall serve as the standard value.

3.3 Designation

The designation of airborne particulate cleanliness for cleanrooms and clean zones shall include:

a) the classification number, expressed as "ISO Class *N*";

b) the occupancy state to which the classification applies;

c) the considered particle size(s), and the related concentration(s), as determined by the classification equation (1) where each considered threshold particle size is in the range from 0,1 µm through 5 µm.

Example designation:

ISO Class 4; operational state; considered sizes:

0,2 µm (2 370 particles/m^3), 1 µm (83 particles/m^3)

The considered particle size(s) for which the concentration(s) will be measured shall be agreed upon by the customer and the supplier.

If measurements are to be made at more than one considered particle size, each larger particle diameter (e.g., D_2) shall be at least 1,5 times the next smaller particle diameter (e.g., D_1).

e.g.: $D_2 \geq 1{,}5 \times D_1$

4 Demonstration of compliance

4.1 Principle

Compliance with air cleanliness (ISO class) requirements specified by the customer is verified by performing specified testing procedures and by providing specified documentation of the results and conditions of testing, as agreed upon by the customer and the supplier.

4.2 Testing

The reference test method for demonstrating compliance is given in annex B. An alternative method having comparable accuracy may be specified, although if no method is specified or agreed upon, the reference method shall be used.

Tests performed to demonstrate compliance shall be conducted using calibrated instruments.

4.3 Airborne particle concentration limits

Upon completion of testing in accordance with 4.2, average particle concentrations and the 95% upper confidence limit (when applicable) shall be calculated using equations shown in annex C.

Average particle concentration(s), calculated in accordance with equation (C.1), shall not exceed the concentration limit(s) determined by use of equation (1) in 3.2, as specified [3.3 c)] for the considered size(s).

In addition, for situations in which the number of sampling locations involved is at least two but not more than nine, the calculation of 95% upper confidence limits in accordance with C.3 shall not exceed the concentration limits established above.

NOTE Worked examples of classification calculations are provided in annex D.

Particle concentrations used for determination of conformance to classification limits shall be measured by the same method for all considered particle sizes.

4.4 Test report

The results from testing each cleanroom or clean zone shall be recorded and submitted as a comprehensive report, along with a statement of compliance or noncompliance with the specified designation of airborne particulate cleanliness classification.

The test report shall include the following:

a) the name and address of the testing organization, and the date on which the test was performed;

b) the number and year of publication of this part of ISO 14644, i.e., ISO 14644-1: date of current issue;

c) a clear identification of the physical location of the cleanroom or clean zone tested (including reference to adjacent areas if necessary), and specific designations for coordinates of all sampling locations;

d) the specified designation criteria for the cleanroom or clean zone, including the ISO classification, the relevant occupancy state(s), and the considered particle size(s);

e) details of the test method used, with any special conditions relating to the test or departures from the test method, and identification of the test instrument and its current calibration certificate;

f) the test results, including particle concentration data for all sampling location coordinates.

NOTE If concentrations of ultrafine particles or macroparticles are quantified, as described in annex E, the pertinent information should be included with the test report.

Annex A
(informative)

Graphical illustration of the classes of Table 1

Figure A.1 depicts the air cleanliness classes of Table 1 in graphical form, for illustration purposes only. The ISO classes of Table 1 are shown as lines representing the class concentration limits for the considered threshold particle sizes. They are based on calculations using equation (1) of 3.2 As the lines only approximate the class limits, they are not to be used to define the limits. Such determinations are made in accordance with equation (1).

The classification lines shown on the graph may not be extrapolated beyond the solid circle symbols, which indicate the minimum and maximum particle size limits acceptable for each of the ISO classes shown.

The classification lines do not represent actual particle size distributions found in cleanrooms and clean zones.

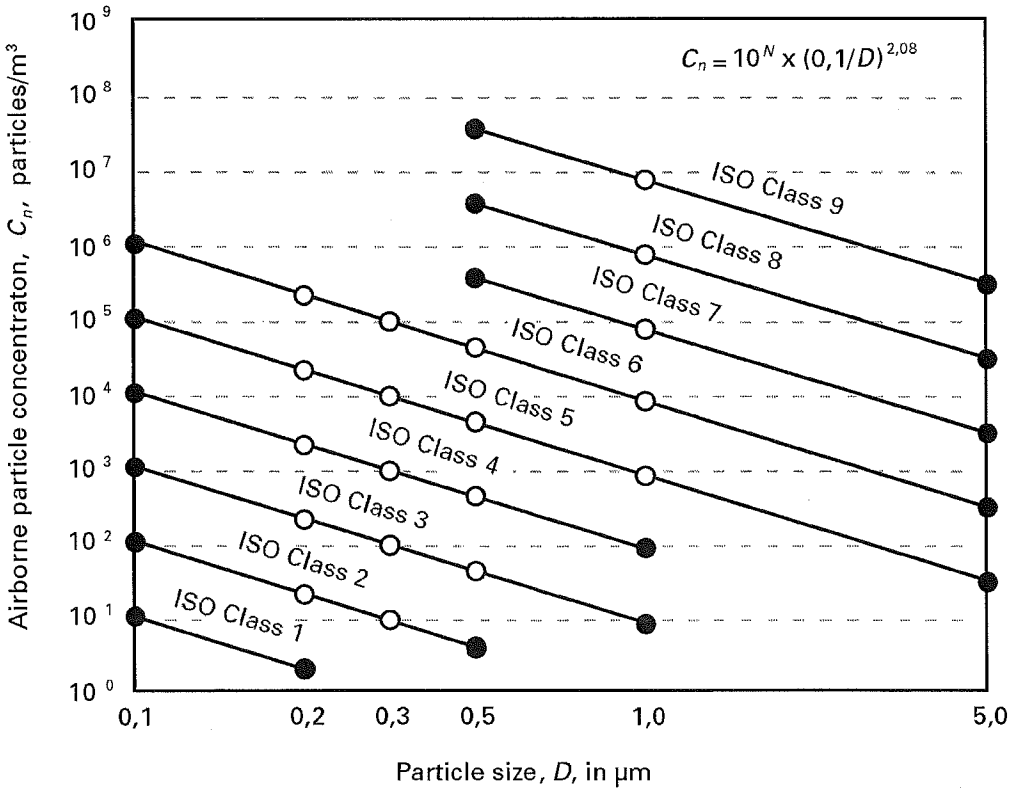

Figure A.1 — Graphical representation of ISO-class concentration limits for selected ISO classes

NOTE 1 C_n represents the maximum permitted concentration (in particles per cubic metre of air) of airborne particles equal to and larger than the considered particle size.

NOTE 2 N represents the specified ISO class number.

Annex B
(normative)

Determination of particulate cleanliness classification using a discrete-particle-counting, light-scattering instrument

B.1 Principle

A discrete-particle-counting, light-scattering instrument is used to determine the concentration of airborne particles, equal to and larger than the specified sizes, at designated sampling locations.

B.2 Apparatus requirements

B.2.1 Particle-counting instrument

Discrete-particle counter (DPC), a light-scattering device having a means of displaying or recording the count and size of discrete particles in air with a size discrimination capability to detect the total particle concentration in the appropriate particle size ranges for the class under consideration, and a suitable sampling system.

B.2.2 Instrument calibration

The instrument shall have a valid calibration certificate; the frequency and method of calibration should be based on current accepted practice.

B.3 Pretest conditions

B.3.1 Preparation for testing

Prior to testing, verify that all aspects of the cleanroom or clean zone that contribute to its operational integrity are complete and functioning in accordance with its performance specification.

Such pretesting may include, for example:

a) airflow volume or velocity tests;

b) air pressure difference test;

c) containment leakage test;

d) installed filter leakage test.

B.3.2 Pretest equipment setup

Perform equipment setup and pretest calibration of the instrument in accordance with the manufacturer's instructions.

B.4 Sampling

B.4.1 Establishment of sampling locations

B.4.1.1

Derive the minimum number of sampling point locations from equation (B.1):

$$N_L = \sqrt{A} \qquad \text{(B.1)}$$

where

N_L is the minimum number of sampling locations (rounded up to a whole number).

A is the area of the cleanroom or clean zone in square metres.

NOTE In the case of unidirectional horizontal airflow, the area A may be considered as the cross section of the moving air perpendicular to the direction of the airflow.

B.4.1.2

Ensure that the sampling locations are evenly distributed throughout the area of the cleanroom or clean zone and positioned at the height of the work activity.

If the customer specifies additional sampling locations, their number and positions shall also be specified.

NOTE Such additional locations may be those considered critical, based on a risk analysis.

B.4.2 Establishment of single sample volume per location

B.4.2.1

At each sampling location, sample a sufficient volume of air that a minimum of 20 particles would be detected if the particle concentration for the largest considered particle size were at the class limit for the designated ISO class.

The single sample volume V_s per location is determined by using equation (B.2):

$$V_s = \frac{20}{C_{n,m}} \times 1\,000 \qquad \text{(B.2)}$$

where

V_s is the minimum single sample volume per location, expressed in litres (except see B.4.2.2).

$C_{n,m}$ is the class limit (number of particles per cubic metre) for the largest considered particle size specified for the relevant class.

20 is the defined number of particles that could be counted if the particle concentration were at the class limit.

NOTE When V_s is very large, the time required for sampling can be substantial. By using the sequential sampling procedure (see annex F), both the required sample volume and the time required to obtain samples may be reduced.

B.4.2.2
The volume sampled at each location shall be at least 2 litres, with a minimum sampling time at each location of 1 min.

B.4.3 Sampling procedure

B.4.3.1
Set up the particle counter (B.2.1) in accordance with the manufacturer's instructions and in compliance with the instrument calibration certificate.

B.4.3.2
The sampling probe shall be positioned pointing into the airflow. If the direction of the airflow being sampled is not controlled or predictable (e.g., nonunidirectional airflow), the inlet of the sampling probe shall be directed vertically upward.

B.4.3.3
Sample the volume of air determined in B.4.2, as a minimum, at each sampling location.

B.4.3.4
Where only one sampling location is required (B.4.1), take a minimum of three single sample volumes (B.4.2) at that location.

B.5 Recording of results

B.5.1 Average concentration of particles at each sampling location

B.5.1.1
Record the result of each sample measurement as the concentration of each of the considered particle size(s) (3.3) appropriate to the relevant classification of air cleanliness.

NOTE Consideration should be given to the requirements of B.6.1 before proceeding with the calculation of the 95% upper confidence limit.

B.5.1.2
When only one sampling location is used, calculate and record the average value of the sample data (B.4.3.4) for each considered particle size.

B.5.1.3
When two or more single sample volumes are taken at a location, compute the average particle concentration for each considered particle size from the individual sample particle concentrations (B.5.1.1), according to the procedure given in C.2, and record the results.

B.5.2 Requirement for computing the 95% upper confidence limit (UCL)

B.5.2.1
When the number of locations sampled is more than one and less than ten, compute the overall mean of the averages, standard deviation, and 95% upper confidence limit from the average particle concentrations for all locations (B.5.1) following the procedure described in C.3.

B.5.2.2
When only a single location is sampled, or when more than nine are sampled, computing the 95% upper confidence limit is not applicable.

B.6 Interpretation of results

B.6.1 Classification requirements
The cleanroom or clean zone is deemed to have met the specified air cleanliness classification if the averages of the particle concentrations measured at each of the locations and, when applicable, the 95% upper confidence limit calculated according to B.5.2, do not exceed the concentration limits determined in accordance with equation (1) of 3.2.

If the results of testing fail to meet the specified air cleanliness classification, testing may be performed at additional, evenly distributed sampling locations. The results of recalculation, including data from the added locations, shall be definitive.

B.6.2 Treatment of outliers
The result of the 95% UCL calculation may fail to meet the specified ISO class designation. If the noncompliance is caused by a single, nonrandom "outlier" value resulting from an erroneous measurement (due to procedural error or equipment malfunction) or from an unusually low particle concentration (due to exceptionally clean air), the outlier may be excluded from the calculation, provided that:

a) the calculation is repeated, including all remaining sampling locations;

b) at least three measurement values remain in the calculation;

c) no more than one measurement value is excluded from the calculation;

d) the suspected cause of the erroneous measurement or low particle concentration is documented and accepted by both the customer and supplier.

NOTE Widely divergent values for particle concentrations among the locations sampled may be reasonable and even intentional, depending on the nature of the application of the clean installation under test.

Annex C
(normative)

Statistical treatment of particle concentration data

C.1 Rationale

This statistical analysis considers only random errors (lack of precision), not errors of a nonrandom nature (e.g. bias associated with erroneous calibration).

C.2 Algorithm for computation of average particle concentration at a location ($\bar{x}_i$)

When multiple samples are taken at a location, equation (C.1) shall be used to determine the average particle concentration at the location. Calculation of the average particle concentration shall be performed for each sampling location at which two or more samples have been taken.

$$\bar{x}_i = \frac{x_{i,1} + x_{i,2} + \ldots + x_{i,n}}{n} \qquad \text{(C.1)}$$

where

$\bar{x}_i$ is the average particle concentration at location i, representing any location.

$x_{i,1}$ to $x_{i,n}$ are the particle concentrations of the individual samples.

n is the number of samples taken at location i.

C.3 Algorithms for computation of 95% upper confidence limit

C.3.1 Principle

This procedure is applicable only if the number of sampling locations is more than one and less than ten. In such circumstances, this procedure shall be used in addition to the algorithm of equation (C.1).

C.3.2 Overall mean of the averages ($\bar{\bar{x}}$)

Using equation (C.2), determine the overall (grand) mean of the averages.

$$\bar{\bar{x}} = \frac{\left(\bar{x}_{i,1} + \bar{x}_{i,2} + \ldots + \bar{x}_{i,m}\right)}{m} \qquad \text{(C.2)}$$

where

$\bar{\bar{x}}$ is the overall mean of the location averages.

$\bar{x}_{i,1}$ to $\bar{x}_{i,m}$ are individual location averages, determined by using equation (C.1).

m is the number of individual location averages.

All individual location averages are equally weighted, regardless of the number of samples taken at any given location.

C.3.3 Standard deviation of the location averages (s)

Using equation (C.3), determine the standard deviation of the location averages.

$$s = \sqrt{\frac{\left(\bar{x}_{i,1} - \bar{\bar{x}}\right)^2 + \left(\bar{x}_{i,2} - \bar{\bar{x}}\right)^2 + \ldots + \left(\bar{x}_{i,m} - \bar{\bar{x}}\right)^2}{(m-1)}} \qquad \text{(C.3)}$$

where

s is the standard deviation of the location averages.

C.3.4 95% upper confidence limit (UCL) for the overall mean

Using equation (C.4), determine the 95% upper confidence limit for the overall mean.

$$95\%\ \text{UCL} = \bar{\bar{x}} + t_{0,95}\left(\frac{s}{\sqrt{m}}\right) \qquad \text{(C.4)}$$

where

$t_{0,95}$ represents the 95th percentile (quantile) of the t distribution, with m–1 degrees of freedom.

Values of the Student's t distribution ($t_{0,95}$) for the 95% UCL are given in Table C.1. Alternatively, Student's t distributions provided in statistical computer programmes are also acceptable.

Table C.1 — Student's t distribution for the 95% upper confidence limit

Number of individual averages (m)	2	3	4	5	6	7-9
t	6,3	2,9	2,4	2,1	2,0	1,9

Annex D
(informative)

Worked examples of classification calculations

D.1 Example 1

D.1.1

The cleanroom under consideration has an area (A) of 80 m^2. Conformance with the specified airborne particulate cleanliness classification is to be determined in the operational state.

The specified air cleanliness classification of the cleanroom is ISO Class 5.

D.1.2

Two considered particle sizes are specified: 0,3 µm (D_1) and 0,5 µm (D_2).

a) Both particle sizes are within the size limitations for ISO Class 5 [see 3.3 c) and Table 1]: 0,1 µm ≤ 0,3 µm, 0,5 µm ≤ 5 µm.

b) Application of the particle size ratio requirement, $D_2 \geq 1{,}5 \times D_1$ [see 3.3 c)], shows compliance: 0,5 µm ≥ (1,5 x 0,3 µm = 0,45 µm).

D.1.3

The maximum permitted airborne particle concentrations are calculated in accordance with equation (1) (see 3.2).

For particles ≥ 0,3 µm (D_1):

$$C_n = \left(\frac{0{,}1}{0{,}3}\right)^{2{,}08} \times 10^5 = 10\,176 \qquad \text{(D.1)}$$

rounded to 10 200 particles/m^3

For particles ≥ 0,5 µm (D_2):

$$C_n = \left(\frac{0{,}1}{0{,}5}\right)^{2{,}08} \times 10^5 = 3\,517 \qquad \text{(D.2)}$$

rounded to 3 520 particles/m^3

D.1.4

The number of sampling point locations are derived in accordance with equation (B.1) (see B.4.1.1):

$$N_L = \sqrt{A} = \sqrt{80} = 8{,}94 \text{ (rounded to 9)} \qquad \text{(D.3)}$$

Therefore the minimum number of sampling locations is nine and, as the number of sampling locations is less than ten, the calculation of the 95% UCL according to annex C is applicable.

D.1.5

The single sample volume, V_s, is calculated in litres in accordance with equation (B.2) (see B.4.2.1):

$$V_s = \frac{20}{C_{n,m}} \times 1\,000 = \frac{20}{3\,517} \times 1\,000 = 5{,}69 \text{ litres} \qquad \text{(D.4)}$$

The result is greater than 2 litres, and the sample volume selected was 28 litres over a period of 1 min (a flow rate commonly available in discrete-particle-counting light-scattering instruments).

This selection was based on:

a) V_s >2 litres (see B.4.2.2)

b) $C_{n,m}$ >20 particles/m^3 (see B.4.2.1)

c) Sampling time ≥ 1 min (see B.4.2.2)

D.1.6

At each sampling location, only one single sample volume (28 litres) is taken (B.4.2.1). The counts obtained from the measurements are recorded (B.5.1.1) below.

Sampling location	Number of particles (≥0,3 µm)	Number of particles (≥0,5 µm)
1	245	21
2	185	24
3	59	0
4	106	7
5	164	22
6	196	25
7	226	23
8	224	37
9	195	19

D.1.7

From the raw data (D.1.6), the number of particles per cubic metre, x_i, is calculated:

Sampling location	$x_i \geq 0{,}3$ µm	$x_i \geq 0{,}5$ µm
1	8 750	750
2	6 607	857
3	2 107	0
4	3 786	250
5	5 857	786
6	7 000	893
7	8 071	821
8	8 000	1 321
9	6 964	679

Each calculated concentration value for 0,3 µm and 0,5 µm is less than the limits established in D.1.3. This satisfies the first part of classification (B.6.1) and therefore calculation of the 95% UCL according to annex C can proceed.

D.1.8

Computation of average concentration in accordance with equation (C.1) (see C.2) is not applicable, as the sample volumes taken were single volumes which represent an average particle concentration at each location. The overall means of the averages are calculated in accordance with equation (C.2) (see C.3.2).

For particles ≥ 0,3 µm:

$$\bar{\bar{x}} = \frac{1}{9}\begin{pmatrix} 8\ 750 + 6\ 607 + 2\ 107 + 3\ 786 \\ +5\ 857 + 7\ 000 + 8\ 071 + 8\ 000 \\ +6\ 964 \end{pmatrix} \qquad (D.5)$$

$$= \frac{1}{9} \times 57\ 142$$

$$= 6\ 349{,}1 \text{ rounded to } 6\ 349 \text{ particles/m}^3$$

For particles ≥ 0,5 µm:

$$\bar{\bar{x}} = \frac{1}{9}\begin{pmatrix} 750 + 857 + 0 + 250 + 786 \\ +893 + 821 + 1\ 321 + 679 \end{pmatrix} \qquad (D.6)$$

$$= \frac{1}{9} \times 6\ 357$$

$$= 706{,}3 \text{ rounded to } 706 \text{ particles/m}^3$$

D.1.9

The standard deviations of the location averages are calculated in accordance with equation (C.3) (see C.3.3).

For particles ≥ 0,3 µm:

$$s^2 = \frac{1}{8}\begin{bmatrix} (8\ 750 - 6\ 349)^2 + (6\ 607 - 6\ 349)^2 \\ +(2\ 107 - 6\ 349)^2 + (3\ 786 - 6\ 349)^2 \\ +(5\ 857 - 6\ 349)^2 + (7\ 000 - 6\ 349)^2 \\ +(8\ 071 - 6\ 349)^2 + (8\ 000 - 6\ 349)^2 \\ +(6\ 964 - 6\ 349)^2 \end{bmatrix} \qquad (D.7)$$

$$= \frac{1}{8} \times 37\ 130\ 073$$

$$= 4\ 641\ 259{,}1 \text{ rounded to } 4\ 641\ 259$$

$$s = \sqrt{4\,641\,259} \qquad (D.8)$$

$$= 2\ 154{,}4 \text{ rounded to } 2\ 154 \text{ particles/m}^3$$

For particles ≥ 0,5 µm:

$$s^2 = \frac{1}{8}\begin{bmatrix} (750 - 706)^2 + (857 - 706)^2 \\ +(0 - 706)^2 + (250 - 706)^2 \\ +(786 - 706)^2 + (893 - 706)^2 \\ +(821 - 706)^2 + (1\ 321 - 706)^2 \\ +(679 - 706)^2 \end{bmatrix} \qquad (D.9)$$

$$= \frac{1}{8} \times 1\ 164\ 657$$

$$= 145\ 582{,}1 \text{ rounded to } 145\ 582$$

$$s = \sqrt{145\,582} \qquad (D.10)$$

$$= 381{,}6 \text{ rounded to } 382 \text{ particles/m}^3$$

D.1.10

The 95% upper confidence limits (UCL) are calculated in accordance with equation (C.4) (see C.3.4). As the number of individual averages is $m = 9$, the t distribution taken from Table C.1 is $t = 1{,}9$.

$$95\%\ \text{UCL}\ (\geq 0{,}3\ \mu\text{m}) = 6\ 349 + 1{,}9\left(\frac{2\ 154}{\sqrt{9}}\right)$$

$$= 7\ 713{,}2 \qquad (D.11)$$

rounded to 7 713 particles/m^3

$$95\%\ \text{UCL}\ (\geq 0{,}5\,\mu\text{m}) = 706 + 1{,}9\left(\frac{382}{\sqrt{9}}\right)$$

$$= 947{,}9 \qquad \text{(D.12)}$$

rounded to 948 particles/m^3

D.1.11

The interpretation of results is carried out according to B.6.1. In D.1.7, it was shown that the particle concentration of each single sample volume is less than the specified class limits. In D.1.10, it was shown that the calculated values of the 95% UCL are also less than the class limits established in D.1.3.

Therefore the airborne particulate cleanliness of the cleanroom meets the required classification.

D.2 Example 2

D.2.1

This example is constructed to show the influence of the 95% UCL calculations on the results.

A cleanroom is specified for a particulate cleanliness of ISO Class 3 in operation. The number of sampling locations has been determined to be five. As the number of sampling locations is more than one and less than ten, the calculation of the 95% UCL according to annex C is applicable.

Only one particle size ($D \geq 0{,}1$ µm) is considered.

D.2.2

The particle concentration limit for ISO Class 3 at ≥ 0,1 µm is taken from Table 1:

$$C_n\ (\geq 0{,}1\ \mu\text{m}) = 1\,000\ \text{particles/m}^3$$

D.2.3

At each sampling location, only one single sample volume is taken (B.5.1.1). The number of particles per cubic metre, x_i, is calculated for each location and recorded below:

Sampling location	$x_i \geq 0{,}1$ µm
1	926
2	958
3	937
4	963
5	214

Each value of the concentration for $D = 0{,}1$ µm is less than the limit established in D.2.2. This result satisfies the first part of classification (B.6.1) and therefore calculation of the 95% UCL according to annex C can proceed.

D.2.4

The overall mean of the averages is calculated in accordance with equation (C.2) (see C.3.2):

$$\bar{\bar{x}} = \frac{1}{5}\,(926 + 958 + 937 + 963 + 214)$$

$$= \frac{1}{5} \times 3\,998 \qquad \text{(D.13)}$$

$$= 799{,}6 \text{ rounded to } 800 \text{ particles/m}^3$$

D.2.5

The standard deviation of the location averages is calculated in accordance with equation (C.3) (see C.3.3):

$$s^2 = \frac{1}{4}\begin{bmatrix} (926 - 800)^2 + (958 - 800)^2 \\ +(937 - 800)^2 + (963 - 800)^2 \\ +(214 - 800)^2 \end{bmatrix} \qquad \text{(D.14)}$$

$$= \frac{1}{4} \times 429\,574$$

$$= 107\,393{,}5 \text{ rounded to } 107\,394$$

$$s = \sqrt{107\,394} = 327{,}7 \qquad \text{(D.15)}$$

rounded to 328 particles/m^3

D.2.6

The 95% UCL is calculated in accordance with equation (C.4) (see C.3.4):

As the number of individual averages is $m = 5$, the t distribution taken from Table C.1 is $t = 2{,}1$.

$$95\%\ \text{UCL} = 800 + 2{,}1\left(\frac{328}{\sqrt{5}}\right) \qquad \text{(D.16)}$$

$$= 1\,108\ \text{particles/m}^3$$

D.2.7

The particle concentrations of all of the single sample volumes are less than the specified classification limit (D.2.2).

Calculation of the 95% upper confidence limit shows, however, that the airborne particulate cleanliness of the cleanroom does *not* meet the specified classification.

This constructed example demonstrates the effect of a single outlying low particle concentration (i.e. location 5) on the result of the 95% UCL test.

Because nonconformance of the air cleanliness classification results from application of the 95% UCL, and is caused by a single, low particle concentration, the procedure described in B.6.2 may be followed to determine whether the nonconformance can be waived.

Annex E
(informative)

Considerations for the counting and sizing of particles outside the size range applicable for classification

E.1 Principle

In some situations, typically those related to specific process requirements, alternative levels of air cleanliness may be specified on the basis of particle populations that are not within the size range applicable to classification. The maximum permitted concentration of such particles and the choice of test method to verify compliance are matters for agreement between the customer and the supplier. Considerations for test methods and prescribed formats for specification are given in E.2 (for U descriptors) and E.3 (for M descriptors).

E.2 Consideration of particles smaller than 0,1 μm (ultrafine particles) — U descriptor

E.2.1. Application

If contamination risks caused by particles smaller than 0,1 μm are to be assessed, sampling devices and measurement procedures appropriate to the specific characteristics of such particles should be employed.

The number of sampling locations should be established in accordance with B.4.1 and the minimum sample volume V_s should be 2 litres (B.4.2.2).

E.2.2 U descriptor format

The ultrafine particle concentration of the U descriptor may be used alone or as a supplement to the airborne particulate cleanliness class. The U descriptor is expressed in the format

"U (*x*; *y*)", where

- *x* is the maximum permitted concentration of ultrafine particles (expressed as ultrafine particles per cubic metre of air);
- *y* is the size in micrometres at which the applicable discrete-particle counter counts such particles with 50% counting efficiency.

EXAMPLE To express a maximum permitted ultrafine particle concentration of 140 000 particles/m^3 in the particle size range ≥ 0,01 μm, the designation would be: "U (140 000; 0,01 μm)".

NOTE 1 Suitable methods of test for concentrations of airborne particles smaller than 0,1 μm are given in *IEST-G-CC1002* [1].

NOTE 2 If the U descriptor designation is used as a supplement to an airborne particulate cleanliness class, the ultrafine particle concentration (*x*) should be not less than the particle concentration limit (particles per cubic metre) applicable to the considered size of 0,1 μm for the specified ISO class.

E.3 Consideration of particles larger than 5 μm (macroparticles) — M descriptor

E.3.1 Application

If contamination risks caused by particles larger than 5 μm are to be assessed, sampling devices and measurement procedures appropriate to the specific characteristics of such particles should be employed.

As particle liberation within the process environment normally dominates the macroparticle fraction of the airborne particle population, the identification of an appropriate sampling device and measurement procedure should be addressed on an application-specific basis. Factors such as the density, shape, volume, and aerodynamic behaviour of the particles need to be taken into account. Also, it may be necessary to put special emphasis on specific components of the total airborne population, such as fibres.

E.3.2 M descriptor format

The M descriptor may be specified independently or as a supplement to the ISO classes of airborne particulate cleanliness. The M descriptor is expressed in the format

"M (*a*; *b*); *c*", where

- *a* is the maximum permitted concentration of macroparticles (expressed as macroparticles per cubic metre of air);
- *b* is the equivalent diameter (or diameters) associated with the specified method for measuring macroparticles (expressed in micrometres);
- *c* is the specified measurement method.

NOTE 1 If the population of airborne particles being sampled contains fibres, they may be accounted for by supplementing the M descriptor with a separate descriptor for fibres, having the format "M_{fibre} (*a*; *b*); *c*".

EXAMPLE 1 To express an airborne particle concentration of 10 000 particles/m^3 in the particle size range of >5 μm based on the use of a time-of-flight aerosol particle counter to determine the aerodynamic diameter of the particles, the designation would be:

"M (10 000; >5 μm); time-of-flight aerosol particle counter".

EXAMPLE 2 To express an airborne particle concentration of 1 000 particles/m^3 in the particle size range of 10 to 20 µm, based on the use of a cascade impactor followed by microscopic sizing and counting, the designation would be:

"M (1 000; 10 µm to 20 µm); cascade impactor followed by microscopic sizing and counting".

NOTE 2 Suitable methods of test for concentrations of airborne particles larger than 5 µm are given in *IEST-G-CC1003* [2].

NOTE 3 If the M descriptor designation is used as a supplement to an airborne particulate cleanliness class, the macroparticle concentration (*a*) should be not greater than the particle concentration limit (particles per cubic metre) applicable to the considered size of 5 µm for the specified ISO class.

Annex F
(informative)

Sequential sampling procedure

F.1 Background and limitations

F.1.1 Background

If the air being sampled is significantly more or significantly less contaminated than the specified class concentration limit for the considered particle size, use of the sequential sampling procedure can reduce sample volumes and sampling times, often dramatically. Some savings may also be realized when the concentration is near the specified limit. Sequential sampling is most appropriate when air cleanliness is expected to quality as ISO Class 4 or cleaner.

NOTE For further information on sequential sampling, see *IEST-G-CC1004* [3].

F.1.2 Limitations

The principal limitations of sequential sampling are:

a) The procedure is only applicable to sampling aimed at a total of 20 particles per measurement, for particles of the considered size at the specified class or concentration limit.

b) Each sample measurement requires supplementary monitoring and data analysis, which can be facilitated through computerized automation.

c) Particle concentrations are not determined as precisely as with conventional sampling procedures, due to the reduced sample volume

F.2 Basis for the procedure

The procedure is based on comparison of real-time cumulative particle counts to reference count values. Reference values are derived from equations for upper and lower limit boundaries:

Upper limit: $C = 3{,}96 + 1{,}03\,E$ (F.1)

Lower limit: $C = -3{,}96 + 1{,}03\,E$ (F.2)

where

C is the observed count;

E is the expected count.

To facilitate comparisons, helpful references have been provided in the form of a graph, Figure F.1, and in tabular form as Table F.1. Either format may be used.

As air is being sampled at each designated location, the running total particle count is continuously compared to reference count limits which are a function of the proportion of the prescribed total volume that has been sampled. If the running total count is less than the lower reference count limit corresponding to the volume that has been sampled, the air being

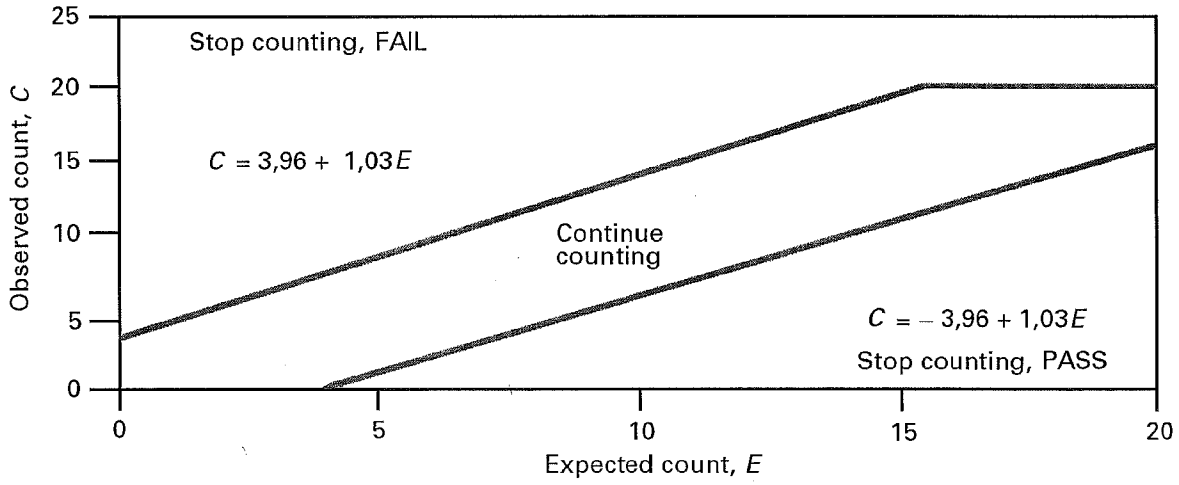

Figure F.1 — Boundaries for pass or fail by the sequential sampling procedure

Table F.1 — Upper and lower limits for time at which *C* observed counts should arrive

FAILS IF COUNT, *C*, COMES EARLIER THAN EXPECTED		PASSES IF COUNT, *C*, COMES LATER THAN EXPECTED	
Fractional time, *t*	Observed Count	Fractional time, *t*	Observed Count
0,001 9	4	0,192 2	0
0,050 5	5	0,240 7	1
0,099 2	6	0,289 3	2
0,147 6	7	0,337 8	3
0,196 1	8	0,386 4	4
0,244 7	9	0,434 9	5
0,293 2	10	0,483 4	6
0,341 7	11	0,532 0	7
0,390 2	12	0,580 5	8
0,438 8	13	0,629 1	9
0,487 3	14	0,667 6	10
0,535 9	15	0,726 2	11
0,584 4	16	0,774 7	12
0,633 0	17	0,823 3	13
0,681 5	18	0,871 8	14
0,730 0	19	0,920 3	15
0,778 6	20	0,968 9	16
1,000 0	21	1,000 0	17

NOTE Fractional times are given as the fraction of total times (t = 1,000 0 at the class limit).

sampled is found to meet the specified class or concentration limit, and sampling is halted.

If the running count exceeds the upper reference count limit corresponding to the volume sampled, the air being sampled fails to meet the specified class or concentration limit, and sampling is halted. As long as the running count remains between the upper and lower limits, sampling continues until the full sample has been accumulated.

In the graph, Figure F.1, the number of observed counts, C, is plotted versus E, the expected number of counts for air being sampled at a rate (volume versus time) that would produce 20 counts in the time it would take to measure a full single sample of air if the concentration were at the specified limit for the considered particle size.

Table F.1 provides an equivalent method, in which the time of the observed count, C, is compared with incremental fractions of the time that would be required to measure a full single sample, as shown in the table. If the count occurs earlier than would be expected from the table, the air being sampled fails to meet the specified limit. If the count occurs later than expected, the air being sampled meets the prescribed limit. At most, 21 comparisons of particle arrival times with the limiting times on the table would be required.

F.3 Procedure for sampling

F.3.1 Sequential sampling references

Two optional comparison techniques are provided for judging the result as data collection proceeds. Progressive computerized analysis of the data is beneficial and recommended.

F.3.2 Graphical sampling comparison

Figure F.1 illustrates the boundaries established in equations (F.1) and (F.2), as truncated by the limitations of $E = 20$, representing the time required to collect a full sample, and $C = 20$, the maximum observed count allowed.

The observed count is plotted versus the expected count for air having a particle concentration precisely at the specified class level. The passage of time corresponds to increasing numbers of expected counts, with $E = 20$ representing the time required

to accumulate a full sample volume if the particle concentration were at the class limit.

The procedure for sequential sampling using Figure F.1 is as follows:

As sampling proceeds, record the number of particles counted as a function of time, and compare the count with the upper and lower limit lines of Figure F.1. If the cumulative observed count crosses the upper line, sampling at the location is stopped and the air is reported to have failed compliance with the specified class limit. If the cumulative observed count crosses the lower line, sampling is stopped and the air passes the specified class limit. If the cumulative observed count remains between the upper and lower lines, sampling will continue.

If the total count is 20 or less at the end of the prescribed sampling period and has not crossed the upper line, the air is judged to have complied with the class limit.

F.3.3 Tabular sampling comparison

Table F.1 provides an equivalent method for use with sequential sampling, also based on equations (F.1) and (F.2). The time, *t*, on the table is assigned a value of "1,000 0" to represent the duration of a complete single sample. The volume of this sample is the volume necessary to provide 20 particles, if the air contains precisely the class limit equivalent concentration of particles of the considered size. The time values listed in the table are the fractional portions of the total time required for accumulation of the entire single sample.

The procedure for sequential sampling using Table F.1 is as follows:

As sampling proceeds, record the number of particles counted as a function of time, and compare the time at which each count is observed with the times shown in the two columns of the table. If a given cumulative observed count occurs earlier than expected, as indicated by comparison with the left-hand column, sampling is stopped and the air is reported to have failed compliance with the specified class limit. If the cumulative observed count occurs later than expected, as indicated by comparison with the right-hand column, sampling is stopped and the air is reported to be in compliance with the specified limit. If the cumulative observed count continuously arrives between the times shown in the two columns, sampling will continue. If counting continues through 21 comparisons with the left-hand column and no count arrives earlier than its expected time, the air passes the specified limit for a full single sample.

Bibliography

[1] *IEST-G-CC1002, Determination of the Concentration of Airborne Ultrafine Particles.* Mount Prospect, Illinois: Institute of Environmental Sciences and Technology (1999)

[2] *IEST-G-CC1003, Measurement of Airborne Macroparticles.* Mount Prospect, Illinois: Institute of Environmental Sciences and Technology (1999)

[3] *IEST-G-CC1004, Sequential Sampling Plan for Use in Classification of the Particulate Cleanliness of Air in Cleanrooms and Clean Zones.* Mount Prospect, Illinois: Institute of Environmental Sciences and Technology (1999)

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EXHIBIT 2

INTERNATIONAL STANDARD

ISO 14644-4

First edition
2001-04-01

EXHIBIT 1

Cleanrooms and associated controlled environments —

Part 4: Design, construction and start-up

Salles propres et environnements maîtrisés apparentés —

Partie 4: Conception, construction et mise en fonctionnement

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Contents

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this part of ISO 14644 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 14644-4 was prepared by Technical Committee ISO/TC 209, *Cleanrooms and associated controlled environments*.

ISO 14644 consists of the following parts, under the general title *Cleanrooms and associated controlled environments*:

— *Part 1: Classification of air cleanliness*

— *Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1*

— *Part 3: Metrology and test methods*

— *Part 4: Design, construction and start-up*

— *Part 5: Operations*

— *Part 6: Vocabulary*

— *Part 7: Separative enclosures (clean air hoods, glove boxes, isolators, mini-environments)*

Users should note that the titles listed for parts 3 and 5 to 7 are working titles at the time of the release of part 4. In the event that one or more of these parts are deleted from the work programme, the remaining parts may be renumbered.

Annexes A to H of this part of ISO 14644 are for information only.

Introduction

Cleanrooms and associated controlled environments provide for the control of airborne particulate contamination to levels appropriate for accomplishing contamination-sensitive activities. Products and processes that benefit from the control of airborne contamination include those in such industries as aerospace, microelectronics, pharmaceuticals, medical devices and healthcare.

This part of ISO 14644 specifies the requirements for the design and construction of cleanroom facilities. It is intended for use by purchasers, suppliers and designers of cleanroom installations and provides a check list of important parameters of performance. Construction guidance is provided, including requirements for start-up and qualification. Basic elements of design and construction needed to ensure continued satisfactory operation are identified through the consideration of relevant aspects of operation and maintenance.

This part of ISO 14644 is one of a series of standards concerned with cleanrooms and associated subjects. Many factors besides design, construction and start-up should be considered in the operation and control of cleanrooms and other controlled environments. These are covered in some detail in other International Standards prepared by ISO/TC 209.

Cleanrooms and associated controlled environments

Part 4: Design, construction and start-up

1 Scope

This part of ISO 14644 specifies requirements for the design and construction of cleanroom installations but does not prescribe specific technological or contractual means to meet these requirements. It is intended for use by purchasers, suppliers and designers of cleanroom installations and provides a checklist of important parameters of performance. Construction guidance is provided, including requirements for start-up and qualification. Basic elements of design and construction needed to ensure continued satisfactory operation are identified through the consideration of relevant aspects of operation and maintenance.

NOTE Further guidance in respect of the above requirements is given in annexes A to H. Other parts of ISO 14644 may provide complementary information.

Application of this part of ISO 14644 is restricted in the following:

— user requirements are represented by purchaser or specifier;

— specific processes to be accommodated in the cleanroom installation are not specified;

— fire and safety regulations are not considered specifically; the appropriate national and local requirements should be respected;

— process media and utility services are only considered with respect to their routing between and in the different zones of cleanliness;

— regarding initial operation and maintenance, only cleanroom construction-specific requirements are considered.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 14644. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 14644 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 14644-1:1999, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness.*

ISO 14644-2:2000, *Cleanrooms and associated controlled environments — Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1.*

ISO 14644-3:— [1], *Cleanrooms and associated controlled environments — Part 3: Metrology and test methods.*

ISO 14698-1:— [1], *Cleanrooms and associated controlled environments — Biocontamination control — Part 1: General principles*

ISO 14698-2:— [1], *Cleanrooms and associated controlled environments — Biocontamination control — Part 2: Evaluation and interpretation of biocontamination data.*

ISO 14698-3:— [1], *Cleanrooms and associated controlled environements — Biocontamination control — Part 3: Measurement of the efficiency of processes of cleaning and/or disinfection of inert surfaces bearing biocontaminated wet soiling or biofilms.*

3 Terms and definitions

For the purposes of this part of ISO 14644, the terms and definitions given in ISO 14644-1 and the following apply.

3.1
changing room
room where people using a cleanroom may change into, or out of, cleanroom apparel

3.2
clean air device
stand-alone equipment for treating and distributing clean air to achieve defined environmental conditions

3.3
cleanliness
condition of a product, surface, device, gas, fluid, etc. with a defined level of contamination

NOTE Contamination can be particulate, non-particulate, biological, molecular or of other consistency.

3.4
commissioning
planned and documented series of inspections, adjustments and tests carried out systematically to set the installation into correct technical operation as specified

3.5
contaminant
any particulate, molecular, non-particulate and biological entity that can adversely affect the product or process

3.6
non-unidirectional airflow
air distribution where the supply air entering the clean zone mixes with the internal air by means of induction

3.7
particle
minute piece of matter with defined physical boundaries

NOTE For classification purposes refer to ISO 14644-1.

3.8
pre-filter
air filter fitted upstream of another filter to reduce the challenge on that filter

---

[1] To be published.

3.9
process core
location at which the process and the interaction between the environment and the process occurs

3.10
start-up
act of preparing and bringing an installation into active service, including all systems

EXAMPLE Systems may include procedures, training requirements, infrastructure, support services, statutory undertakings requirements.

3.11
unidirectional airflow
controlled airflow through the entire cross-section of a clean zone with a steady velocity and approximately parallel streamlines

NOTE This type of airflow results in a directed transport of particles from the clean zone.

4 Requirements

4.1 The parameters listed in 4.2 to 4.18 shall be defined and agreed between purchaser and supplier:

NOTE In the requirements stated below, references are made to annexes A to H which are for information only.

4.2 The number, edition and date of publication of this part of ISO 14644 shall be given.

4.3 The role of other relevant parties to the project (e.g. consultants, designers, regulatory authorities, service organizations) shall be established (see examples in annex C).

4.4 The general purpose for which the cleanroom is to be used, the operations to be carried out therein and any constraint imposed by the operating requirements (see examples in annexes A, B and D).

4.5 The required airborne particulate cleanliness class or demands for cleanliness in accordance with the relevant International Standard (ISO 14644-1, ISO 14698-1, ISO 14698-2 and ISO 14698-3) (see examples in annex B).

4.6 The critical environmental parameters, including their specified set points, alert and action levels to be measured to ensure compliance, together with the measurement methods to be used, including calibration (ISO 14644-2 and ISO 14644-3) (see examples in annex F).

4.7 The contamination control concept, including installation, operating and performance criteria, to be used to achieve the required cleanliness level (see examples in annex A).

4.8 The methods of measurement, control, monitoring and documentation required to meet the parameters agreed (see examples in annexes C and F).

4.9 The entry or exit of equipment, apparatus, supplies and personnel required to support the installation (see examples in annex D).

4.10 The specified occupancy states selected from "as-built", "at-rest" and "operational" under which the required parameters shall be achieved and maintained including variations with time, and the methods of control (see examples in annex C).

4.11 The layout and configuration of the installation (see examples in annex D).

4.12 Critical dimensions and mass restrictions, including those related to available space (see examples in annex D).

4.13 The process and product requirements that affect the installation (see examples in annexes B and G).

4.14 The process equipment list with utility requirements (see examples in annexes D, E and H).

4.15 The maintenance requirements of the installation (see examples in annexes D and E).

4.16 The assignment of tasks for the preparation, approval, execution, supervision, documentation, statement of criteria, basis of design, detailed design, construction, testing, commissioning and qualification (including the performance and witnessing) of tests (see examples in annexes E and G).

4.17 The identification and evaluation of external environmental influences (see examples in annex H).

4.18 Additional information required by the particular application (see examples in annex H).

5 Planning and design

5.1 Planning procedure

5.1.1 A project plan shall be developed, in consultation with the user and all other involved parties, to define the requirements of the products, the processes and the scope of the installation.

5.1.2 In order to determine the needs of an installation, a process equipment list shall be compiled, and shall include the critical requirements for each piece of process equipment.

5.1.3 Diversity factors shall be defined, considering peak and average demand for each utility and environmental control system.

NOTE A system may include multiple subsystems which require individual diversity-factor determination.

5.1.4 A contamination control concept shall be developed for each zone of an installation (see examples in annex A).

5.1.5 The specifications as defined in clause 4 shall be reviewed and refined based on financial and timescale requirements.

5.1.6 The project plan shall include the following elements:

a) design documentation with support calculations;

b) cost evaluation;

c) timescale evaluation;

d) an outline of anticipated project complications;

e) design options with records of advantages and disadvantages and any recommendations;

f) a review of maintenance requirements of the installation;

g) a review of the degree of flexibility to be included in the installation;

h) a review of the stand-by capacities to be included in the installation;

i) a review of the constructability of the design of the installation;

j) a quality plan.

The use of a quality system, such as the ISO 9000 family of international standards (e.g. ISO 9000 and ISO 9001), should be considered, in conjunction with industry-specific quality assurance strategies.

5.1.7 The completed project plan shall be reviewed and agreed upon between purchaser and supplier.

5.2 Design

5.2.1 The design shall accommodate all of the relevant product and process requirements in conjunction with the selected contamination control concept (see examples in annex A).

5.2.2 The purchaser and supplier shall formally accept the design in accordance with predetermined acceptance criteria.

5.2.3 The design shall conform to an agreed list of requirements, such as building, environmental and safety regulations, good manufacturing practice guidelines (e.g. ISO 14001 and ISO 14004).

The design should be reviewed at periodic stages of development, including final completion, to ensure compliance with the specifications and the acceptance criteria.

6 Construction and start-up

6.1 Construction of an installation shall comply with the drawings and specifications.

6.2 Any changes required during the course of construction shall be checked for acceptance, approved and documented prior to implementation of the change in accordance with a change control procedure.

6.3 Construction work, whether performed at a manufacturing location or *in situ*, shall observe the specific contamination control requirements of the quality plan.

6.4 A clean construction protocol and cleaning procedures shall be developed as part of the quality plan and enforced to achieve the specified contamination control requirements. Security and access control is essential to maintain the clean construction protocol.

6.5 The cleaning methods and methods to determine and approve the achieved cleanliness shall be defined and documented in the quality plan.

6.6 The cleaning of the air systems shall be specified and shall be carried out at assembly, before initial operation and whenever rebuilding work, repair work and maintenance work are performed.

6.7 In the case of start-up of new installations or re-starting existing installations after repair or modification, final cleaning of the cleanroom is necessary and provisions shall be made for the removal of adherent, imported or released contamination.

6.8 Before commencing any operational activities, the complete and satisfactory function of the installation shall be determined by tests carried out in accordance with clause 7.

NOTE In the case of packaged units, such as clean air devices, a manufacturer's certificate of compliance with the requirements of this part of ISO 14644 may be sufficient, provided that the supplier is qualified (i.e. knowledgeable of or competent in cleanroom requirements) and the risk of damage during transport, storage and installation can be controlled adequately.

6.9 During acceptance testing, commissioning and initial operation, the personnel in charge of the installation shall be trained. Testing, approval of the installation and training shall include all relevant practices for proper cleanroom operation, maintenance and in-process control. The responsibility for providing training shall be defined.

When training is carried out, all relevant persons such as operators, maintenance and service personnel should be included.

7 Testing and approval

7.1 General

During and upon completion of the construction of an installation, an agreed series of documented tests shall be specified and undertaken prior to operational use of the installation. Annex C gives examples of the design, testing and approval processes.

7.2 Construction approval

A systematic range of inspections, adjustments, measurements and tests shall be carried out to ensure that each part of the installation complies with the design requirements.

7.3 Functional approval

A series of tests and measurements shall be carried out to determine that all parts of the installation operate together to achieve the required conditions in the "as-built" or "at-rest" states.

7.4 Operational approval

A series of tests and measurements shall be carried out to determine that the complete installation achieves the required "operational" performance with the specified process or activity functioning, and with the specified number of personnel present working in the agreed manner.

8 Documentation

8.1 General

Details of a completed installation (including instrumentation calibration) and all operation and maintenance procedures shall be documented. Documents shall be made readily available to all personnel responsible for start-up, operation and maintenance of the installation.

Such personnel should fully understand the documentation.

8.2 Record of an installation

Details of the completed installation shall be provided and shall contain:

a) a description of the installation and its function;

b) a set of final and approved performance test data, derived from the tests carried out in accordance with clause 7 of this part of ISO 14644, recording the values of all conditions defined in the specification for the installation and achieved during the commissioning, testing and start-up procedures;

c) a set of drawings, diagrams (e.g. layout of wiring, piping and instrumentation) and specifications describing the completed and approved "as-built" installation and its components;

d) a list of parts and equipment and any recommendation for stocking spare parts.

8.3 Operational instructions

Each installation or system shall be provided with a clear set of operating instructions. Such operating instructions shall contain:

a) schedules of checks and inspections to be completed prior to the start-up of an installation;

b) schedules of the acceptance range of the critical performance parameters specified;

c) procedures to start and stop the installation under normal and failure mode situations;

d) procedures to be adopted in the event of alert or action levels being reached.

8.4 Instructions for performance monitoring

Performance-monitoring of an installation is essential to demonstrate satisfactory operation. Documentation shall include:

a) test and measurement frequency;

b) description of test and measurement methods, (or reference to standards and guidelines);

c) action plan in the event of non-compliance;

d) frequency required for assembly, analysis and retention of performance data to enable trends to be analysed.

8.5 Maintenance instructions

Maintenance shall be implemented in accordance with a specified method and programme.

Maintenance and repairs shall be carried out during the construction, commissioning, testing, start-up and normal operation of an installation. The following items shall be considered:

a) definition of safety procedures prior to carrying out maintenance or repairs;

b) specification of maintenance actions to be taken when the acceptance range of any critical performance parameter is exceeded;

c) agreed definition of permitted adjustments;

d) methods of making permitted adjustments;

e) methods of checking and calibrating control, safety and monitoring devices;

f) requirements for checking and replacing all wearing parts (e.g. driving belts, bearings, filters);

g) specification for cleaning of the installation or components prior to, during and after maintenance work;

h) definition of actions, procedures and tests required after maintenance is completed;

i) inclusion of any user-specific or relevant regulatory authority requirements.

8.6 Maintenance record

A documented record of any maintenance carried out upon the installation during construction, commissioning and start-up shall be maintained. The following items shall form part of the record:

a) definition of the maintenance tasks;

b) identification and approval of personnel undertaking the maintenance;

c) date of carrying out the maintenance;

d) a condition report prior to undertaking the maintenance;

e) a list of spare parts used;

f) a report upon completion of the maintenance.

8.7 Record of operation and maintenance training

A documented record of training shall be maintained. The following items shall form part of the record:

a) definition of the training content;

b) identification of personnel providing and receiving the training;

c) training date and duration;

d) a report upon each period of training as it is completed.

Annex A
(informative)

Control and segregation concepts

A.1 Contamination control zones

For economic, technical and operational reasons, clean zones are often enclosed or surrounded by further zones of lower cleanliness classification. This can allow the zones with the highest cleanliness demands to be reduced to the minimum size. Movement of material and personnel between adjacent clean zones gives rise to the risk of contamination transfer, therefore special attention should be paid to the detailed layout and management of material and personnel flow.

Figure A.1 illustrates an example of a contamination control concept. In this configuration, the clean zone would be regarded as a more stringently controlled portion of the cleanroom.

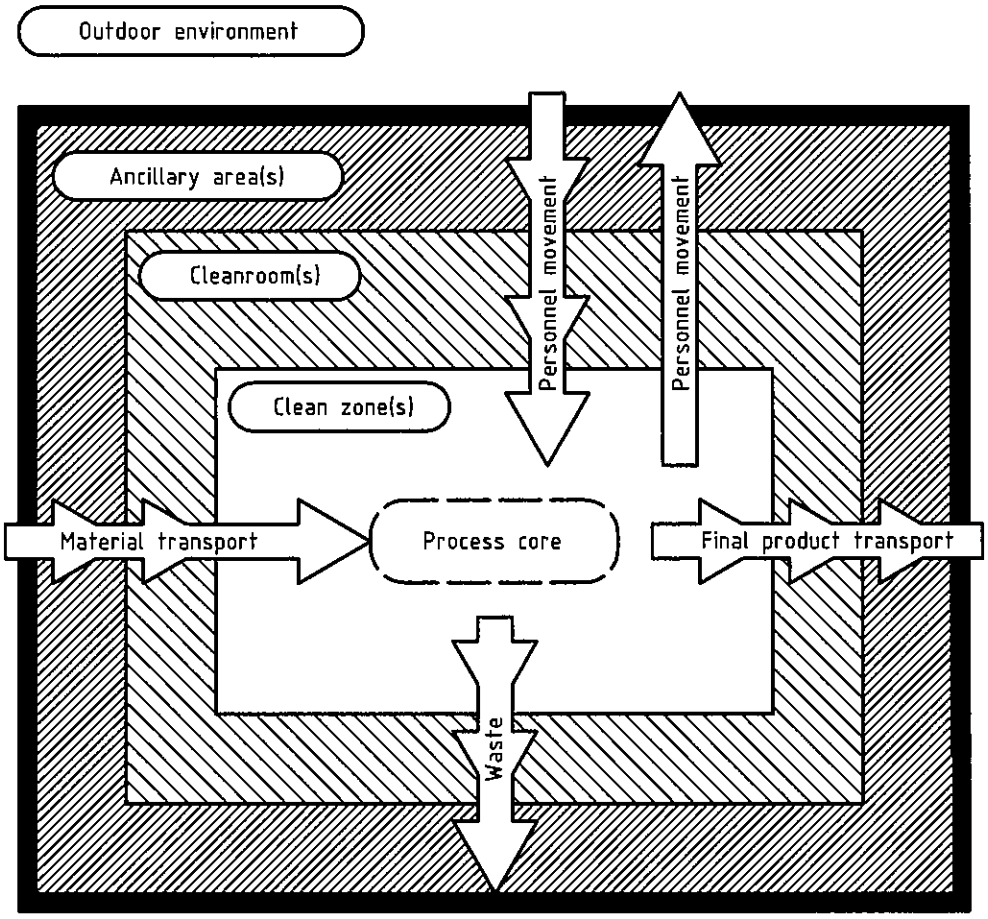


Figure A.1 — Shell-like contamination control concept

A.2 Airflow patterns

A.2.1 Cleanroom airflow patterns can be categorized as either unidirectional or non-unidirectional. When a combination of the two is used it is frequently called mixed airflow. Airflow patterns for cleanrooms of ISO Class 5 and cleaner in operation are often unidirectional, while non-unidirectional and mixed flow is typical for cleanrooms of ISO Class 6 and less clean in operation.

A.2.2 Unidirectional airflow may be either vertical or horizontal (see Figure A.2). Both types of unidirectional airflow rely upon a final filtered air supply and air return inlets which are nearly opposite one another in order to maintain the airstream in as straight a flow pattern as possible. In both designs, the important design feature is the ability to ensure that the airflow pattern is disrupted as little as possible at the process core.

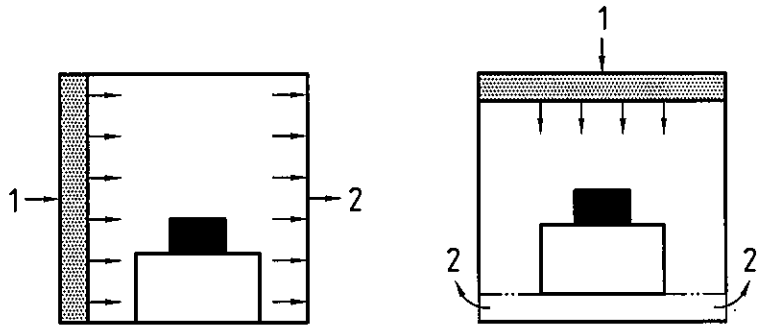
In a working plane perpendicular to the clean airflow, all positions offer the same cleanliness level. Hence, horizontally integrated or distributed processes require vertical airflow and vertically integrated processes require horizontal airflow. Working positions immediately adjacent to the clean air supply offer optimal contamination control conditions, because working positions downstream of these positions may be subject to particles generated upstream. Personnel placement should be therefore downstream of clean processing.

A.2.3 In non-unidirectional airflow cleanrooms, air flows from filter outlets located in multiple positions distributed across the inlet plane and is returned through remote locations. Filter outlets may be distributed at equal intervals throughout the cleanroom or clean zone or grouped over the process cores. The location of filter outlets is important for the cleanroom performance. The final filter location may be remote, but special precautions should be taken to avoid contamination ingress between these filters and the cleanroom (e.g. monitoring of the surface cleanliness and airtightness of ventilation ducts and supply air inlets to avoid induction of contamination as well as the deployment of decontamination procedures). While return air locations in non-unidirectional airflow systems are not as critical as those in unidirectional applications, care should be taken to distribute the returns, as is done with the supplies, to minimize dead zones within the cleanroom.

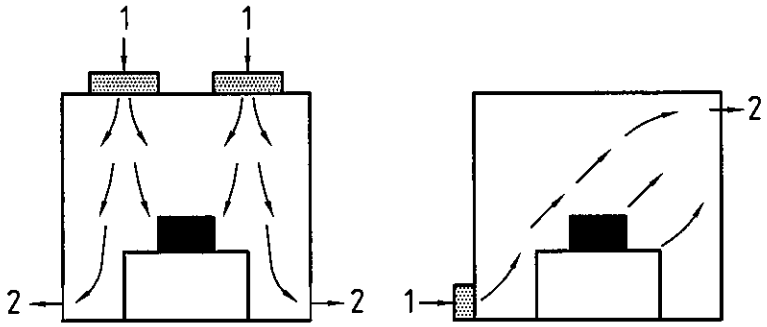
A.2.4 Mixed-airflow cleanrooms combine both unidirectional and non-unidirectional airflow in the same room.

NOTE Some special designs are available that provide protection to specific working zones by other managed airflow techniques.

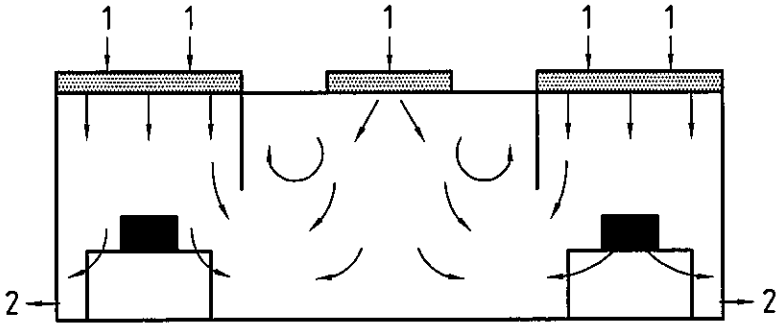
Figure A.2 gives examples that illustrate the different airflow patterns in cleanrooms. (Thermal effects are not considered.)



a) Unidirectional airflow



b) Non-unidirectional airflow



c) Mixed airflow

Key

1 Supply air

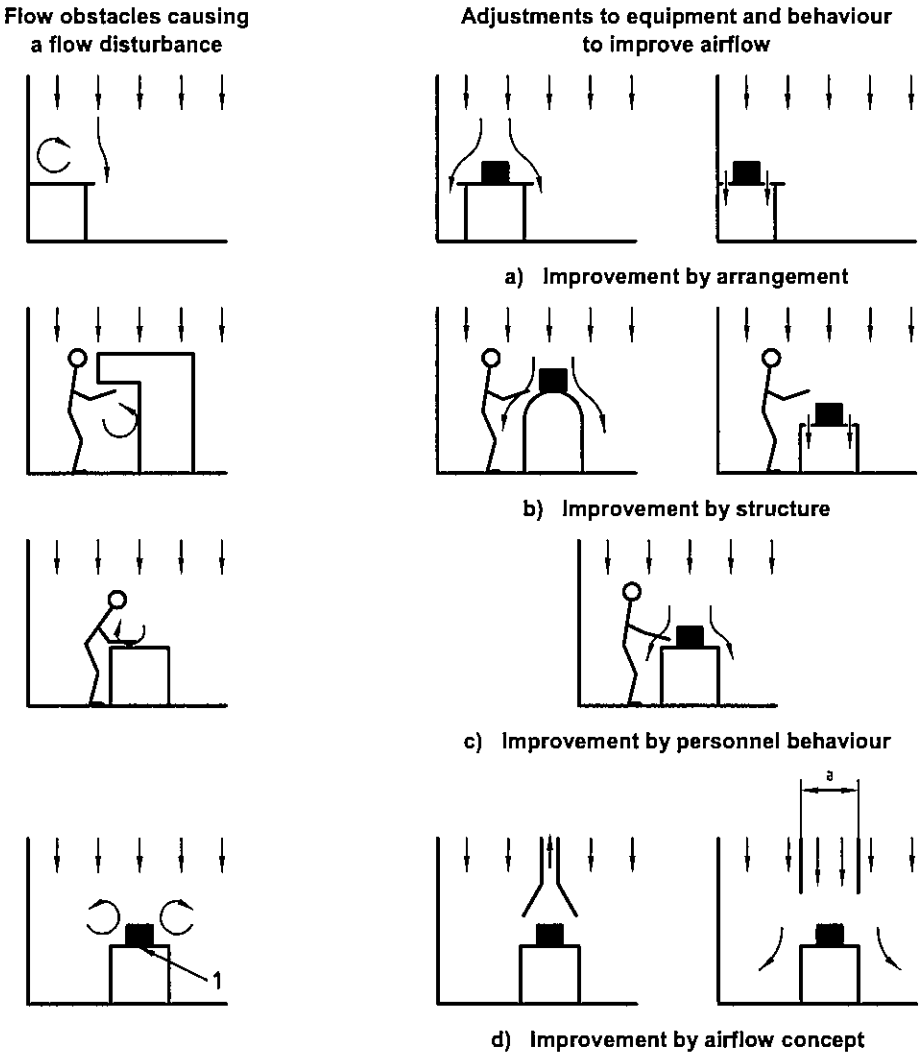
2 Return air

Figure A.2 — Airflow patterns in cleanrooms

A.3 Disturbance of unidirectional airflow

In unidirectional airflow cleanrooms, the design of physical obstacles such as the process equipment, and the operating procedures, personnel movements and product handling, should consider basic aerodynamic requirements to prevent serious turbulence in the vicinity of the contamination-sensitive activity. Appropriate measures should be taken to avoid flow disturbances and cross-contamination between different work stations.

Figure A.3 shows the influence of physical obstacles (on the left) and appropriate measures for minimizing the impact of these (on the right).



Key

1 Heat source

a Local increase in air velocity.

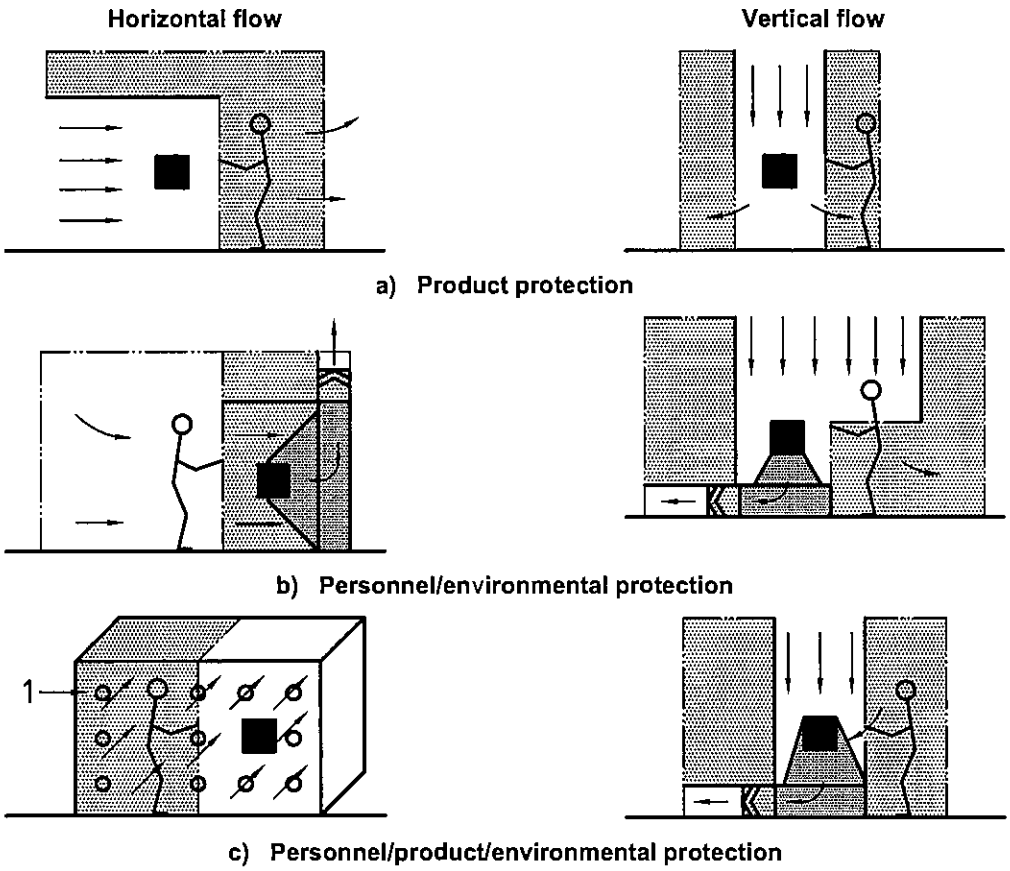
Figure A.3 — Influence of personnel and objects on unidirectional airflow

A.4 Contamination control concepts

To select the proper technique for a given contamination control problem, Figures A.4 and A.5 show some different contamination control concepts that may be considered.

The transfer of contaminants into a zone protecting a process and/or personnel can be prevented by using aerodynamic measures, i.e. by arrangement and flow direction (Figure A.4), or by physical barriers, i.e. by both active and passive isolation (Figure A.5), if any contact between product and operator/environment is to be prevented.

If necessary, process exhaust should be treated to prevent contamination of outdoor environment.

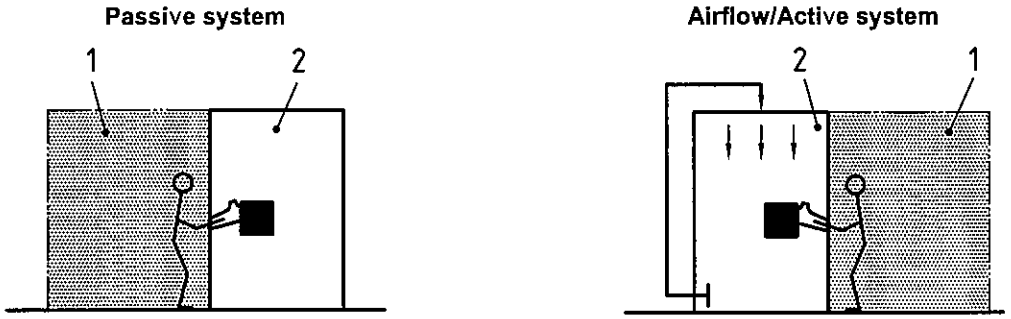


Key

1 Flow direction perpendicular to graphic plane

NOTE In particular cases (e.g. dry atmosphere, shielding and protecting gas or extreme temperatures), the gas flow routing chosen should be adapted to the process.

Figure A.4 — Contamination control concepts using aerodynamic measures



Key

1 Personnel safety zone

2 Product protection zone

Figure A.5 — Contamination control concepts using physical segregation for product and personnel protection

A.5 Concepts to achieve segregation of cleanrooms and clean zones

A.5.1 General

A suite of cleanrooms can consist of multiple rooms with different requirements for contamination control. The objective of the design can be to protect the product or process, or to contain the product, and in some cases a combination of these requirements. In order to protect cleanrooms from contamination from adjacent less clean spaces, the cleanroom should be maintained at a higher static pressure than the adjacent spaces, or alternatively a controlling air velocity should be established across the leakage paths between the spaces flowing from the cleaner to the less clean space.The converse can be applied to contain a hazard. In both cases, an impervious physical barrier can be used as an alternative.

The quantity of make-up air should be sufficient for ventilation purposes and to compensate for the leakage of air from the boundary of the cleanrooms or clean zones and any exhaust air for other purposes.

The following comparison of three basic concepts has been prepared to facilitate the selection of a suitable cleanroom or clean zone segregation concept.

A.5.2 Displacement concept (low pressure differential, high airflow)

A low pressure differential can effectively separate clean and less clean adjacent zones, i.e. by means of a low turbulent "displacement" airflow, e.g. larger than 0,2 m/s (see Figure A.6).

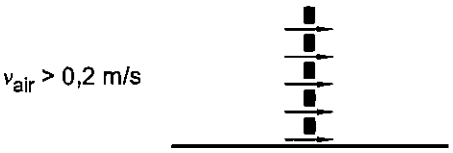


Figure A.6 — Displacement concept

Displacement airflow velocity should be typically above 0,2 m/s, from the cleaner zones towards the less clean zones. The necessary airflow velocity should be selected considering important conditions such as physical obstacles, heat sources, exhausts and contamination sources.

A.5.3 Pressure differential concept (high pressure differential, low airflow)

A pressure differential exists across the barrier between the cleaner zone towards the less clean zone. A high pressure differential between adjacent zones can be easily controlled but care is recommended to avoid unacceptable turbulence (see Figure A.7).

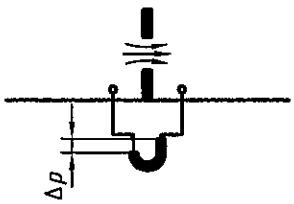
The pressure differential should be of sufficient magnitude and stable to prevent reversal of airflow direction from that intended. The pressure differential concept should be carefully considered, whether used alone or in combination with other contamination control techniques and concepts.

The pressure differential between adjacent cleanrooms or clean zones of different cleanliness level should lie typically in the range of 5 Pa to 20 Pa, to allow doors to be opened and to avoid unintended cross-flows due to turbulence.

The static pressure between cleanrooms of different class, and cleanrooms and unclassified areas can be established and maintained using various airflow balancing techniques. These include both active/automated and passive/manual systems that are configured to adjust the relative quantities of air that are delivered and removed from each space by the ducted air system, air transfer system and losses.

In situations when pressure differentials at the lower end of this range are accepted, special precautions should be taken to ensure accurate measurement of separating flow or pressure and to prove the stability of the installation.

NOTE Flow visualization, either experimentally or by computation, can be used to demonstrate both the effectiveness of the displacement flow concept and the pressure differential concept.



Δp = 5 Pa to 20 Pa

Figure A.7 — High pressure differential concept

A.5.4 Physical barrier concept

This concept involves the use of an impervious barrier to prevent contamination transfer to a clean zone from a less clean zone.

NOTE All three concepts can be applied in the healthcare products, semiconductor, food and other industries.

Annex B
(informative)

Classification examples

B.1 Healthcare products

For the manufacture of healthcare products, a frequently used correlation of typical manufacturing applications and cleanroom classification levels is given (see Table B.1). At the process core, the sterile product is filled through an aseptic assembly of components in a clean zone, controlled for particulate and microbiological contamination.

To access the process core, both the personnel and the process materials traverse several shells of increasing cleanliness (decreasing particulate concentrations). Personnel moving between various zones of different levels of cleanliness may change garments between zones, in accordance with the requirements of the zone that they are entering. Materials that enter each zone should be treated in a method appropriate to the level to be entered to remove particulate and/or microbiological contamination.

Table B.1 — Cleanroom examples for aseptic processing of healthcare products

Air cleanliness class (ISO Class) in operation [a]	Airflow type[b]	Average, airflow velocity[c] m/s	Examples of applications
5 (at ⩾ 0,5 µm)	U	> 0,2	Aseptic processing[d]
7 (at ⩾ 0,5 µm)	N or M	na	Other processing zones directly supporting aseptic processing
8 (at ⩾ 0,5 µm)	N or M	na	Support zones of aseptic processing, including controlled preparation zones

NOTE 1 Application-specific classification requirements should take into account other relevant regulations.

NOTE 2 na = not applicable

[a] Occupancy states associated with the ISO Class should be defined and agreed in advance of establishing optimum design conditions.

[b] When airflow type is listed, it represents the airflow characteristics for cleanrooms of that class: U = unidirectional; N = non-unidirectional; M = mixed (combination of U and N).

[c] Average airflow velocity is the way that unidirectional airflow in cleanrooms is usually specified. The requirement on unidirectional airflow velocity will depend on specific application factors such as temperature, and configuration of the controlled space and the items to be protected. Displacement airflow velocity should be typically above 0,2 m/s.

[d] Where operator protection is required to ensure safe handling of hazardous materials, the use of segregation concepts (see examples in annex A) or appropriate safety cabinets and devices should be considered.

B.2 Microelectronics

In the microelectronics industry, the minimum device feature size or film thickness dictates the target level of contamination control and the corresponding cleanliness class.

The cleanliness class with the lowest particle concentration is often selected with reference to the critical particle size. The critical particle size (often assumed to be 1/10th of the minimum feature size) is used to help select the required cleanliness classification for the cleanroom.

Determination of cleanroom or clean zone cleanliness for different process cores is based upon the probability of contamination and the potential for device failure.

For example, **photolithography** is a process which involves exposure of wafers to the environment with a high probability of contamination and also a very high potential for device failure when contamination occurs. Accordingly, protection in microelectronics for this type of risk often involves the use of physical barriers which protect process cores in order to lower particle concentrations or alter other process parameters (e.g. temperature, humidity, pressure).

Work zones are zones where wafers or die are handled by people and/or automated handling equipment, and the potential for contamination is high if the product is directly exposed to the environment. The most common responses for the protection of the product within work zones involve unidirectional flow, minimizing occupancy and production load per cubic meter of cleanroom, segregating personnel from exposed product(s) increasingly including barrier techniques. Work zones are most commonly separated from adjacent, less critical zones, by physical barriers and airflow.

Utility zones are zones where the non-operator interface portions of the wafer processing equipment are typically located. In the utility zones it is typical that work in progress is not exposed to the environment. The utility zone of a process core is usually adjacent to its corresponding work zone.

Service zones are zones where neither product nor process equipment are located, but service zones are sited next to work or utility zones to help separate the cleaner zones from the less clean zone (see Table B.2).

B.3 Influence of cleanroom clothing

The number of personnel and the type of cleanroom clothing may require specific consideration with respect to particle emission (see relevant parts of this International Standard, e.g. ISO 14644-5).

Table B.2 — Examples for microelectronic cleanrooms

Air cleanliness class[a] (ISO Class) in operation	Airflow type[b]	Average, airflow velocity[c] m/s	Air changes per hour[d] $m^3/m^2 \cdot h$	Examples of applications
2	U	0,3 to 0,5	na	Photolithography, semiconductor processing zone[e]
3	U	0,3 to 0,5	na	Work zones, semiconductor processing zone
4	U	0,3 to 0,5	na	Work zones, multilayer masks processing, fabrication of compact discs, semiconductor service zone, utility zones
5	U	0,2 to 0,5	na	Work zones, multilayer masks processing, fabrication of compact discs, semiconductor service zone, utility zones
6	N or M[f]	na	70 to 160	Utility zones, multilayer processing, semiconductor service zones
7	N or M	na	30 to 70	Service zones, surface treatment
8	N or M	na	10 to 20	Service zones

NOTE na = not applicable

[a] Occupancy states associated with the ISO Class should be defined and agreed in advance of establishing optimum design conditions.

[b] When airflow type is listed, it represents the airflow characteristics for cleanrooms of that class: U = unidirectional; N = non-unidirectional; M = mixed (combination of U and N).

[c] Average airflow velocity is the way that unidirectional airflow in cleanrooms usually is specified. The requirement on unidirectional airflow velocity will depend on local parameters such as geometry and thermals. It is not necessarily the filter face velocity.

[d] Air changes per hour is the way that non-unidirectional and mixed airflow is specified. The suggested air changes are related to a room height of 3,0 meter.

[e] Impervious barrier techniques should be considered.

[f] With effective separation between contamination source and zones to be protected. Could be a physical or airflow barrier.

Annex C
(informative)

Approval of an installation

C.1 Test preparation and final cleaning

Prior to carrying out any inspection, test or measurement procedure, running systems should be allowed time to reach stability; this period of time should be agreed upon in advance. Tests should be of sufficient duration to demonstrate consistent performance (see clause 4, and examples in annex H).

Prior to the fitting of filters and after cleaning as described in E.1.2/E.3.3 in annex E has been completed, all ducts, walls, ceilings, floors and installed fittings should be cleaned to remove contamination which could prejudice the classification of the cleanroom.

Following cleaning, the final filters should be fitted and the commissioning tests conducted to demonstrate compliance.

C.2 Inspection, tests and approvals

C.2.1 General

In order to demonstrate that an installation is complete in every respect and performs to meet all contamination control requirements included in clause 4, a specific range of inspections and tests should be carried out upon the installation in question. Typical activities are identified in C.2.2 to C.2.5 and Figure C.1 for graphic representation.

C.2.2 Concept and design approval

A check should be carried out to ensure that the concept, design, and developed details satisfy the agreements between the purchaser and supplier. Review should include at least:

a) contamination control concept;

b) layout of equipment;

c) description of the installation;

d) schemes and drawings;

e) incorporation of all other agreed requirements.

C.2.3 Construction and installation approval

C.2.3.1 Construction approval (at supplier's site)

A check should be carried out to ensure that the components and assemblies comply with the design. The check should include at least the following items:

a) inspection and testing for completeness and quality according to specification;

b) approval for compliance with safety regulations, ergonomic requirements, relevant guidelines and normative regulations;

c) approval of certificates.

C.2.3.2 Installation approval (at the site of the installation)

A check should be carried out to ensure that the construction of the installation complies with the design. The check should include in addition to C.2.3.1 at least the following items:

a) completeness of the installation;

b) interfaces with other suppliers;

c) correct function of utilities and auxiliary equipment;

d) calibration of all control, monitoring, warning and alarm systems;

e) fitting and in-situ testing of final filters;

f) proving the reserve capacity of the air treatment system;

g) testing enclosure for leakage;

h) confirming that the proportion of recirculation to make-up air complies with the design specification;

i) surface cleanliness and suitability of the installation (see examples in annex E);

j) spare parts package.

C.2.4 Functional approval

After having completed the checks and approvals according to C.2.3.2, at least the following functional tests should be performed:

a) determine clean zone segregation;

b) measure and record contamination control recovery time;

c) determine ability to maintain temperature and relative humidity requirements;

d) determine airborne particulate cleanliness class;

e) where appropriate, determine particulate surface cleanliness and microbiological contamination levels;

f) determine light and noise levels;

g) demonstrate and record airflow patterns and air change rate if necessary.

C.2.5 Operational approval (equipment installed in a manner agreed in advance)

Certain of the previous tests may be repeated to determine compliance with the operational conditions, namely:

a) confirm clean zone segregation regime;

b) determine ability to maintain temperature and relative humidity;

c) determine airborne particulate cleanliness class;

d) where appropriate, determine particulate surface cleanliness and microbiological contamination levels;

e) check the completeness of documentation according to clause 8.

For compliance-related issues, refer to ISO 14644-2; for microbiological-related issues, refer to ISO 14698-1, ISO 14698-2 and ISO 14698-3; for testing-related issues and for operational-related issues, refer to other relevant parts of this International Standard.

C.3 Reports

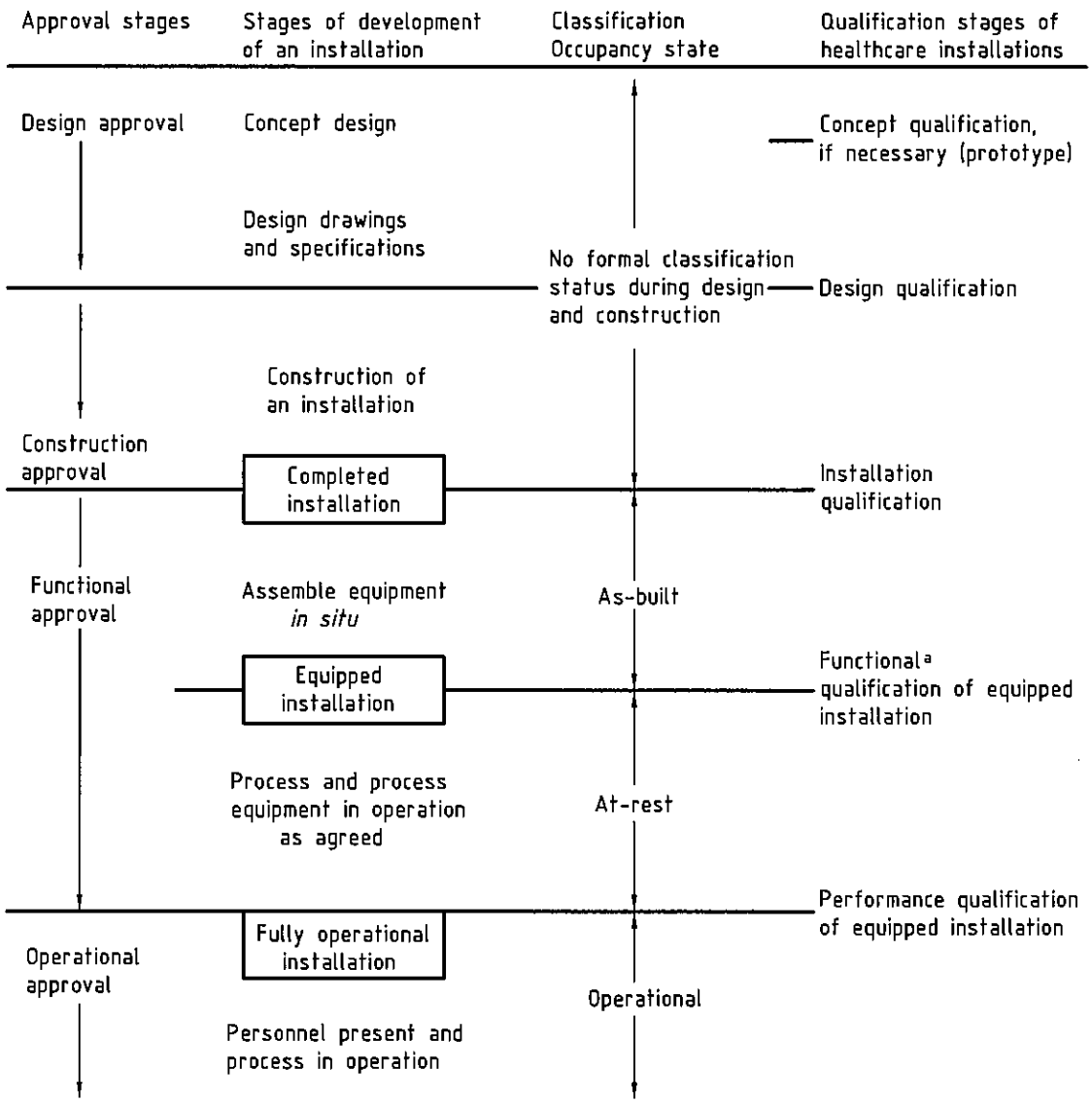
The reports of the tests should be presented in a documented manual. This manual should include:

a) supplier's test documentation;

b) calibration certificates of instrumentation used;

c) relevant drawings and as-installed details;

d) witnessed verification of compliance with specification.



[a] Often used: operational.

Figure C.1 — Approval of an installation

Figure C.1 indicates a logical sequence for and relationship between approvals, stages of development and the formal classification occupancy state of an installation. Terminology may vary in specific industries, through established usage or regulatory requirement. Figure C.1 shows the qualification sequence frequently used in healthcare industry applications, in relation to the stages of construction and approval.

Annex D
(informative)

Layout of an installation

D.1 General considerations

D.1.1 Size

The size of a cleanroom should be kept to the minimum practicable, allowing for any future requirements. In general, if a large amount of space is required, it should be divided into several zones or rooms, with or without physical barriers.

NOTE It is recognized that the presence of people, and activity, within a cleanroom can generate both contamination and disturbance of airflow. Annex B provides examples of installation configurations to control these phenomena. Annex A discusses contamination control concepts in which airflow and the physical configuration of a workstation or other critical discrete areas are managed to obviate or minimize exchange of contamination between product and its environment, including people in the immediate proximity.

D.1.2 Workstation siting and organization

Within the cleanroom, critical workstations or areas of risk should be sited away from entries and exits, major traffic pathways and other features which may cause disruption of the airflow pattern and higher levels of contamination.

In horizontal-flow cleanrooms, the siting of workstations should be such that the clean work which is to be performed receives clean air from the appropriate source, without flow disturbance or contamination from personnel movements or adjacent work.

When operations that require different degrees of cleanliness are to be carried out in an area swept by horizontal unidirectional airflow, less clean operations should be sited downstream of cleaner operations, insofar as it can be determined that this arrangement will not compromise the maintaining of target conditions for any critical points.

D.1.3 Ancillary areas and adjacent cleanrooms

Consideration should be given to the location and integration of ancillary areas such as service and utility, cleaning, preparation, toilet and refreshment facilities, in order to avoid compromise of the critical conditions maintained within the cleanrooms. Pressure or flow differentials, access and communication arrangements (such as airlocks, speech panels and intercoms), enclosure sealing (notably material joints, equipment and utility penetrations) should be executed so that cross-contamination from less clean zones does not compromise the cleaner zones. Layout should combine with effective training and management of personnel behaviour to minimize disturbance and cross-contamination due to movement between ancillary areas and cleanrooms.

D.1.4 Utility services and ancillary equipment

D.1.4.1 General

Utility services provided for the cleanroom should be designed, located and installed such that the cleanroom is not compromised by contamination from such services.

In general, exposed piping, tubing and cable runs within the cleanroom should be minimized, as these may present problems for adequate cleaning, and may be sources of damage by contact with cleanroom garments, wipes, etc. This should be balanced against the potential for contamination within protective housings, covers, etc., which may also hinder disinfection or fumigation. Where possible, consideration should be given to the routing of such services

in external service areas or ducts. Means should be provided for the effective removal of waste and contamination generated within such spaces.

Power take-off points, taps and connections should be designed and installed to facilitate regular cleaning, and to avoid the build-up of contamination in or behind blanking covers. Wherever possible, maintenance activities should be performed outside the cleanroom. Pressure or flow differentials, access arrangements (notably airlocks and transfer hatches), enclosure sealing (notably material joints, equipment and utility penetrations) should be executed so that cross-contamination from ancillary areas does not compromise the cleanroom.

The number, type and location of utility services should be agreed between the purchaser and supplier.

D.1.4.2 Vacuum-cleaning equipment

Vacuum-cleaning equipment, either portable or built-in, should be provided to ensure that particulate contamination can be removed during periodic cleaning, and to ensure that contamination generated by any operation that cannot reasonably be conducted outside the cleanroom can be removed efficiently, and with appropriate frequency.

Where a permanent vacuum-cleaning system is provided, the exhaust and fan should be sited outside the cleanroom. The connection sockets in the cleanroom should be blanked off when not in use. The airflow through the vacuum chamber should not compromise the differential pressure or the airflow configuration of the cleanroom.

When portable vacuum equipment is used, it should be fitted with an exhaust filter of at least the same efficiency as that filtering the environmental air supply, and care should be taken to consider the influence upon air patterns in the cleanroom.

D.1.4.3 Sprinkler systems

Fire control systems present special problems, notably in the routing of supply piping containing a fire suppressant medium, whether water, chemical substance or gas, which is a potential contaminant of the cleanrooms, and a potential source of damage to the components of the installation, in the event of accidental or deliberate release.

When sprinkler piping is to run above ceilings, careful consideration should be given to its routing, in relation to the equipment and operations sited in the cleanroom below. Adequate access should be provided for maintenance and modification, and consideration should be given to provision of means to collect and evacuate fluid leaked or released above the ceiling.

Penetration of walls or ceilings for supply to sprinkler points should be sealed as appropriate, like all other penetrations of the cleanroom. The sprinkler heads themselves should be situated and shaped for minimum intrusion into the cleanroom, and for minimal disturbance of clean airflow, insofar as this is compatible with their primary safety function. Where disturbance is inevitable, appropriate measures should be taken to avoid any undesirable effect upon the required integrity of the cleanroom conditions.

D.1.5 Communication systems

Wherever practical, communication systems should be provided in order to minimize movement of personnel into and out of the cleanroom. Windows, speech panels, intercoms, data links and telephones are suitable means of communication. They should be selected to be compatible with the cleanroom class and application considerations.

D.1.6 Glazing

Where windows to the outside are a requirement, care should be taken, in design and fitting, to avoid undue heat loss, solar gain and condensation. The use of windows to adjoining inside spaces should be considered, to allow observation of activity within the room, without entry. Windows should be non-opening and sealed. Double glazing can be used to achieve flush fitting, and also enables provision of interstitial shutters or blinds. The use of exposed blinds within a cleanroom should be avoided.

D.2 Access

D.2.1 General

The number of openings connecting the cleanroom to outside, or adjoining, areas should be minimized.

Effective means should be taken to minimize the contamination arising from the entry or exit of personnel or material, or from air movement. Normal (non-emergency) access to or from the cleanroom should be through airlocks for both personnel and material.

D.2.2 Airlocks

In order to maintain pressure differential and integrity of the controlled space during entry and exit, airlocks or transfer hatches (pass-throughs) are normally required.

Precautions should be taken to ensure that entry and exit doors associated with an airlock are not opened simultaneously. Clear windows can be provided at both points to allow a line-of-sight view between them. Consideration should be given to the use of electrical or mechanical interlock systems including audio-visual indicators.

Barrier benches or other clear demarcation systems, together with appropriate decontamination devices and procedures, should be employed within an airlock system for the passage of material. The passage of material and personnel can be segregated.

D.2.3 Emergency exits

Emergency exits should be provided with means to show that they have been opened.

D.2.4 Changing rooms

D.2.4.1 General

Changing rooms are specialized airlocks for the entry and exit of personnel to and from a cleanroom. They should include sufficient space for their function, and, depending on the cleanroom quality, facilities for donning and removing specialized garments, and may include washing, disinfection facilities, etc. Special contamination control equipment such as air showers, shoe cleaners and adhesive floor materials may be provided at the point(s) of entry and exit to the cleanroom.

Separation of the personnel entering from those leaving the cleanroom via the changing room should be ensured. This can be achieved by separation in time, or by providing physically separate entry and exit routes.

Where hazardous materials are processed, a separate changing and decontamination route should be considered.

D.2.4.2 Changing room control and configuration

Changing rooms should be provided with a level of contamination control and environmental control that ensures the integrity of the cleanroom. Similarly, the methods and equipment for storage of garments and equipment for use in the cleanroom should be commensurate with the required cleanliness and contamination protection required by the contamination-sensitive operation. To provide the required protection, consideration should be given to three functional zones of the changing room:

a) at the changing room entry: access from ancillary areas (either directly or via an airlock) appropriate for removal, storage, disposal and/or redonning of garments not permitted within the cleanroom;

b) the transition zone: area where garments or personal equipment dedicated to the cleanroom are stored, donned or removed, as appropriate;

c) the inspection/access zone: area where inspection of the completed gowning process is accomplished and which provides access to the cleanroom either directly or via an airlock.

The three functional zones may be separated by a physical barrier (e.g. a stepover bench or airlock) as appropriate to the operation and use of the changing room. The three zones should be established, such that the zone closest to the cleanroom provides a high degree of assurance, and that minimal adverse impact is caused by access or gowning procedures implemented in the adjacent zone.

D.2.4.3 Facilities in changing rooms

The features provided in the changing room are particular to the cleanroom that the changing room serves.

The following requirements should be defined:

— number of people passing through the gowning procedure, both in the absolute, and at any one time;

— the gowning procedure (i.e. what garments are to be taken off and put on, whether these are reusable or single-use, the required protocol to ensure garment cleanliness and to avoid cross-contamination);

— the frequency of garment replacement.

Consideration should be given to the following provisions in the changing room:

a) storage and disposal of garments;

b) storage before use, provision and disposal of consumable items and accessories (e.g. gloves, masks, protective glasses, overshoes);

c) storage of personal items;

d) hand-washing and -drying or other decontamination processes;

e) prominent display or posting of gowning sequence, with clear instructions;

f) full-length mirrors to check effective fit.

Annex E
(informative)

Construction and materials

E.1 Selection of materials

E.1.1 General

The materials used in the construction of the installation should be selected and applied to meet the requirements of the installation, and should take into account the following:

a) the cleanliness class;

b) effects of abrasion and impact;

c) cleaning and disinfection methods and frequencies;

d) chemical/microbiological attack and corrosion.

Materials which may tend to break down or to shed particles should only be used when they are effectively encapsulated and protected.

Consideration should be given to the chemical compatibility of all materials used with the operating requirements of the installation. This may, for instance, influence the choice of adhesives and sealing mastics for surface-finishing work, or of materials used for filter assembly and sealing.

All surfaces which come into contact with air supplied to the interior of the cleanroom or clean zone may by their nature or condition influence the quality of the air supplied to the contamination-sensitive zones. For this reason, materials and finishes intended for the internal surfaces of the complete air-handling system should be critically assessed and specifically approved for this purpose.

All exposed surfaces of equipment, furnishings and material present within the cleanroom or clean zone should meet the same criteria as the exposed structural elements of the installation.

Further details of specific performance criteria follow.

E.1.2 Surface cleanliness and cleanability of materials of construction

All exposed materials should be suitable for effective and frequent cleaning and disinfection, and offer no surface asperities or porosity which are likely to allow retention of particulate and chemical contamination, or the development of microbiological contamination. Methods for selecting, applying and controlling suitable procedures for cleaning and disinfection are indicated in ISO 14698-1 and ISO 14698-3, and other relevant parts of this International Standard. Appropriate methods for assessing and monitoring surface cleanliness (for instance in terms of releasable particulate, biological and chemical contamination) should be selected and approved for the application. Exposed materials should be selected with due consideration of their resistance to the mechanical and chemical effects of the intended methods of cleaning and disinfection, in order to remain smooth, non-porous, abrasion- and stain-resistant (see also E.1.4 and E.3.3).

Walls, floors and ceilings in cleanrooms and in clean zones should be designed and constructed in such a way that the surfaces are accessible for cleaning. In a room, this generally includes the walls, floors, ceilings and doors, the inlet side of air diffusers and floor drain, etc. (see examples in annex G).

When it is necessary to wipe down or wash walls, floors or ceilings on a frequent basis, consideration of the selection of materials should include careful evaluation of the junction and intersection details, and in particular the avoidance of places where moisture can be trapped or lie on surfaces.

E.1.3 Control of electrostatic charging and discharge

Accumulation of electrostatic charge, and subsequent electrostatic discharge, can present a risk of hazards such as explosion (in the presence of powders or gases), device damage (e.g. damage to electronic or optical components), or excessive attraction of particles to surfaces contributing to physical, chemical and microbiological contamination.

Where the above risks cause concern, materials used in the construction of installations should neither generate nor hold a significant static charge. This significant value will be specific to each application, and should be clearly specified by the purchaser. Certain processes may require particular conditions in terms of environmental humidity, in order to minimize the generation of electrostatic charge. Annex F provides further guidance on this technique. It should be noted that the most favourable humidity conditions for avoidance of electrostatic charge accumulation may conflict with other requirements of the process, or project objectives. A solution should be agreed, which achieves an acceptable compromise. Certain applications may require the use of conductive or static dissipative materials in order to minimize the influence of any induced static charge.

To protect electrostatically sensitive components the resistance to earth should be in the range of $R_E = 10^4\ \Omega$ to $10^7\ \Omega$. Care should be taken to protect the personnel against risk of electrocution. Earthing should be considered, with a site transition resistance $R_{ST} = 5 \times 10^4\ \Omega$. The "ideal" range of resistance is therefore between the site transition resistance $R_{ST} = 5 \times 10^4\ \Omega$ and the mass resistance $R_E = 10^7\ \Omega$.

The required electrical characteristics for flooring are valid for the entire structure or composite of materials used as a floor, and should be measured regularly to monitor potential loss of performance through ageing. Limit values of 2 kV (applicable to accumulated surface charge) should not be exceeded. Monitoring of wall conductivity should be carried out regularly and after modifications or repairs.

E.1.4 Internal finishes, durability and maintainability

In the completed installation, all internal surfaces should be finished suitably smooth, non-porous and free from cracks, cavities, steps and ledges. The design and construction should be such that the number of steps, ledges, cavities and similar features where contamination could collect is minimized. The number of corners should also be kept to a minimum, particularly internal corners. Corners and junctions may be radiused, especially at floor-to-wall and wall-to-wall junctions, so that effective cleaning is facilitated. The finish should be compatible with the mechanical and chemical effects of the intended methods of cleaning and disinfection.

Materials used for internal finishes should be maintained to ensure that they consistently retain the performance qualities consistent with the cleanliness class of the installation. This may require regular maintenance procedures and repairs. Consideration of maintenance and repair methods and disruption impact should form part of the material selection criteria. Full lifecycle cost and contamination risk analysis procedures should be considered.

E.2 Considerations for specific components

E.2.1 Ceilings, walls and floors

E.2.1.1 Basic requirements

Wall, ceiling and floor elements should comply with all relevant regulations concerning fire protection, sound and thermal insulation. Surface finish and assembly details should be compatible with the specified cleaning methods. In order to avoid glare, consideration should be given to the interaction of surface colour and finish with the intended lighting conditions. Airlocks, gowning rooms and material passage points should normally have at least the same requirements as the cleaner of the zones they serve. In the case of equipment and material transfer airlocks, decontamination and "cleandown" procedures may impose special requirements.

NOTE There are many acceptable methods and materials for constructing cleanrooms ranging from *in situ* construction to fully prefabricated site-assembled systems. The basic options are summarized as follows:

a) Prefabricated site-assembled systems and *in situ* construction:

   1) wet construction with applied surface finish,

   2) dry construction with applied surface finish.

b) *In situ* assembly:

   1) pre-finished engineered components,

   2) modular pre-finished panel system.

Combinations of these basic construction options can also be used.

The choice of method of construction of an installation should take into account not only the contamination control and operational requirements, but also matters relating to the construction location (e.g. construction and finishing skills available); considerations influenced by the available building envelope in which the installation is located, such as available height, load-bearing capability, deflection of structures; maintenance constraints and requirements such as "walk-on-ceiling" capability, etc.

E.2.1.2 Ceilings

Ceilings should be sealed, to prevent ingress of air bearing particles, or other contaminants, from the ceiling void. Filters, filter frames, filter housings and diffusers mounted in the ceiling should be sealed. Penetration points (e.g. for utility services, sprinklers and lighting) should be kept to the minimum required, and be sealed. Consideration should be given to the location and configuration of components such as lights and sprinklers to avoid disturbance of the intended airflow.

E.2.1.3 Walls and wall systems

Materials and surface finishes should meet all general requirements for their application. Particular consideration should be given to impact and abrasion resistance, especially in those locations exposed to frequent passage of trolleys, carts or personnel carrying material likely to contact exposed surfaces of walls and doors. Suitable rubbing strips or protective bars may constitute satisfactory protection of otherwise vulnerable material.

Some applications may require that walls or wall panels be sealed to prevent exchange of contaminants with surrounding areas. Cover strips or seals between panels should be smooth, with rounded edges (some applications require flush fitting) to facilitate efficient cleaning and limit retention of contaminants. Particular attention should be paid to smoothness and effective sealing of utility services or other penetrations.

Where glazing is required, in walls or doors, it should be of the non-opening type. Consideration should be given to the use of double glazing, with airtight seal, which can enable flush mounting on both sides. If blinds or shutters are required, these should be fitted outside the clean zone, or between the glazed elements of double glazing. Glazing frames should be smooth. Where flush fitting is not required, rounded edges or sloping surfaces should be considered.

Doors should present as few horizontal surfaces as possible, with particular attention being paid to the minimization of steps and ledges in the door surface. Thresholds should be avoided. Consideration should be given to the minimization of abrasion in the mechanical elements of the door (e.g. latches, locks and hinges), and also between the door and its frame and the floor. Door handles, where required, should be smooth, non-snagging and easy to clean. Consideration should be given to the use of push plates, automatic openings, or appropriate door-swing direction where contamination transfer is a concern.

E.2.1.4 Floors

Floors or floor coverings should be non-porous, slip-resistant, abrasion-resistant, conductive if necessary; resistant to the chemicals they will encounter in use (both cleaning and disinfection products, and accidental spillage of process fluids) and easy to clean. The floor should support the specified static and dynamic loads with the required durability. The floor complex should provide the appropriate electrostatic characteristics.

E.2.2 Air-handling systems

Attention should be paid to minimizing the contamination generated, retained and released throughout the air-handling system, in all components and surfaces in contact with the system air, in order that an excessive load is not placed on the filtration system. Ducts should be manufactured from materials with corrosion-resistant and non-flaking properties, or should be given suitable surface treatment to prevent release of contaminants from the duct to the air passing through. If there is no terminal filter outlet provided, the quality and integrity of the system downstream of the final filter is more important. The effects of leakage from air-handling systems should be considered.

E.2.3 Fittings in airlocks

Fittings in airlocks and gowning rooms should present as few horizontal surfaces as possible. For example consideration should be given to the use of hanging rails and perforated shelf boards rather than closed lockers. Exposed surfaces should satisfy criteria similar to those specified for the interior of the cleanroom and clean zone, and may require additional specifications to ensure durability in this application.

E.2.4 Ancillary areas

These should have no direct connection to the cleanroom, except for emergency exits. Exposed surfaces in these areas should be chosen with a particular concern for durability and ease of maintenance.

E.3 Construction and assembly

E.3.1 General

Construction work should comply with the drawings and specifications, and the agreed quality plan. Any changes required during the construction phase should be checked for acceptance, approved and documented prior to their implementation (see also examples in annex C).

E.3.2 Material management during construction

All components and materials for use in the construction and subsequent maintenance of the installation should be manufactured, packed, transported, stored and inspected before use in such a manner as to ensure their suitability for their intended use.

E.3.3 Cleanliness and cleaning during construction and start-up

Many tasks involved in construction and assembly intrinsically generate contamination. A clean construction protocol should be developed and enforced to satisfy and achieve the specified contamination control objectives. Particular attention should be paid to the scheduling of tasks which are the greatest sources of contamination, such that those tasks are accomplished before tasks which are lesser sources of contamination or more contamination-sensitive.

During construction, measures should be taken to ensure that contamination generated in the course of assembly and construction work is contained and removed, so as to limit undue contamination of surrounding areas. Appropriate means of containment may include the use of temporary screens and walls, and pressurization of critical zones, with provisional use of temporary "sacrificial" filters in the air-handling system(s). Such filters, installed to protect clean volumes (clean environment and air-handling systems) from outside contaminants, and to permit their initial pressurization and operation, are intended to be removed and replaced by filters of the appropriate grade at the agreed stage or stages of start-up, before construction approval and subsequent operational use of the installation.

Continual or frequent cleaning should be planned, undertaken and controlled as specified, with the aim of preventing undue build-up of contaminants in any part of the installation, and so facilitating the essential final cleaning before start-up (see also clause 6 and E.1.2).

It may be useful to effect initial cleaning of components, and those preparation or assembly tasks which it is not absolutely necessary to perform as part of definitive construction *in situ*, in a separate or intermediate zone between the point of reception on-site, and the final point of construction. Such procedures can contribute significantly to the reduction of contamination in all parts of the installation, though they are of special value where subsequent access and cleaning would be difficult or impossible.

E.4 Materials of construction

Typical surface materials are:

a) For walls and ceilings:

- sheets of stainless steel;
- anodized aluminium;
- polymer sheets or coating.

mounted on appropriate substrates or construction

b) For floors:

- polymer coating or sheets;
- tiles with appropriate sealed joints.

Selection of materials should include consideration of the chemical, thermal and mechanical stresses during operation (production, setup, cleaning and decontamination as well as conductivity and outgassing characteristics). Additionally, flexibility, functionality, durability, aesthetics and maintainability should be considered by customer and supplier.

Annex F
(informative)

Environmental control of cleanrooms

F.1 Design

F.1.1 Requirements for environmental control vary with each application. Therefore the purchaser should state which criteria are important when specifying a cleanroom. The lists given in this annex are not exhaustive and should be supplemented as required.

F.1.2 The design of the environmental systems should take into account the following:

a) the contamination control concept chosen;

b) product quality requirements;

c) capital and operating costs (life cycle costing);

d) energy conservation;

e) safety;

f) health and comfort of personnel;

g) needs and constraints imposed by equipment and processes;

h) reliability, ease of operation and maintenance;

i) environmental issues (e.g. handling of waste and packaging);

j) regulatory requirements.

F.2 Temperature and humidity

F.2.1 The set point and variation limits of temperature (in degrees Celsius) and relative humidity (in percent saturation) which may depend on special process requirements should be specified for the performance of the cleanroom.

F.2.2 Temperature control should be provided for:

a) processes;

b) equipment and materials;

c) stable conditions for personnel wearing cleanroom garments selected to suit the class of cleanliness specified.

In general terms, heat loads from lighting are high and stable; personnel loads vary; the heat generated by process operations (e.g. heat-sealing, soldering, welding, heat-treating and heating pressure vessels) is usually high and variable.

F.2.3 The large quantities of air required for contamination control facilitate the offsetting of internal heat gains at an acceptable rate of response from the temperature control system. However, areas of concentration of heat-

producing equipment and supply-air patterns should be analysed to determine the acceptability of resulting temperature gradients and contamination control.

F.2.4 Humidity control should be provided for:

a) manufacturing processes;

b) equipment and materials;

c) the reduction of electrostatic charges;

d) personnel comfort in conjunction with temperature control mentioned above.

F.2.5 In cleanroom installations, humidity control is affected more by external influences (such as weather changes) than by variations in moisture generation within the space. If processes involving evaporation should take place within the cleanroom installation, they should be confined within ventilated enclosures. Precautions should be taken to control static electricity effects. Some manufacturing processes (such as vacuum tube manufacture and tabletting) require relative humidities (R.H.) lower than 35 %. As indicated in annex E, consideration should be given also to selection of materials which minimize electrostatic effects. If the humidity in a confined space is low, static charges may be higher than in an area with higher humidity.

F.2.6 Temperature and humidity levels for personnel comfort should be defined for these specific installations. A typical set range for relative humidity is < 65 % R.H. to > 30 % R.H. Outside this range, suitable measures should be considered to meet process and personnel requirements. Specific guidance to adjust temperature specifications to cleanroom garments used is given in ISO 7730.

F.2.7 The locations at which temperatures and relative humidities require to be measured should be specified.

F.2.8 The outside conditions under which the system is required to operate should be specified taking into account the intended operational mode.

F.2.9 The amount of heat and moisture generated in the cleanroom, the location of sources and the nature of their dynamic variation should be specified.

F.3 Lighting

F.3.1 The lighting levels and uniformities required within the various parts of the installation should be specified, together with the methods used to assess them.

F.3.2 The colour rendering of light should be specified by the purchaser, as it has a significant effect on the comfort of personnel and, in many cases, the processes being carried out, especially photosensitive processes.

F.3.3 The lighting system should be consistent with the effective operation of the cleanroom. Light fittings should have no areas from which contamination may be released. The use of sealed or flush fittings should be considered. For unidirectional airflow applications, the design and positioning of the light fitting and associated diffuser should be such as to minimize or negate turbulence. The light fittings should be serviceable in a manner such that the integrity of the cleanroom is not violated and excessive contamination is not produced. The effect of glare should be considered within the context of the work being carried out.

F.4 Noise and vibration

F.4.1 General

Noise and vibration limits should be specified, if required, according to a specific process or other requirements. Consideration should be given to

a) site selection: vibration, soils, and future site developments;

b) structural design: cleanroom floor support, stiffness, isolation joints;

c) mechanical design: equipment selection, system design, performance specifications, vibration isolation systems, noise control systems (internal and external);

d) architectural layout: building and installation layout, plant areas, service systems.

F.4.2 Sound pressure level

The selected sound pressure level should be based on the requirements with regard to both the comfort and safety of the personnel and consideration of the background sound pressure level created in the environment (e.g. other equipment). A typical A-weighted sound pressure level range for cleanroom installations lies between 55 dB and 65 dB. Some applications may require lower levels or may tolerate higher levels. Noise control measurements should be carried out in accordance with ISO 3746.

F.4.3 Mechanical vibration

F.4.3.1 Vibration is an important consideration in cleanroom installations, since it can have an adverse influence on processes, human comfort and service life of equipment and systems.

F.4.3.2 Vibration in cleanrooms should be minimized, or the source isolated, using methods such as high quality fans and vibration control equipment.

F.4.3.3 When vibration control is required, the permissible levels should be defined using ISO 1940-1 and ISO 10816-1.

F.5 Energy conservation

Consideration may be given to incorporating in the design energy conservation considerations, such as provisions to reduce or close down temperature and humidity control and to reduce airflow during periods in which there is no activity. The ability to recover operating conditions in a defined recovery period should be demonstrated.

Annex G
(informative)

Control of air cleanliness

G.1 Air filtration systems

Air filtration systems including filter elements, mounting frames, housings, gaskets, sealants and clamping systems should be selected to suit both the cleanliness level required and the conditions associated with their use and installation test requirements in the system. Specific air filtration standards should be used for filter selection. Three basic stages of air filtration are recommended:

a) prefiltering of the outside air to ensure adequate quality of air supply to the air conditioning plant;

b) secondary filtering in the air conditioning plant to protect the final filters;

c) final filtering before cleanroom supply.

G.2 Secondary filtration

It should be understood that unless adequate secondary filtration is provided before the final filters supplying cleanrooms, several problems may arise. These problems include the following:

a) the desired class of air cleanliness may not be achieved;

b) the high frequency of final filter changing may become unacceptable;

c) undesirable particulate and microbiological contamination of the product may occur.

G.3 Application

The designer should evaluate the performance of the primary and secondary air filters used in cleanroom air conditioning systems to suit each application. Consideration should be given to the use of filters for chemical and molecular decontamination (e.g. activated carbon) and configurations for exhaust air filtration to protect the outdoor environment.

G.4 Energy conservation

For energy conservation reasons, airflow of the ventilation systems may be reduced to low levels during non-operating periods. If, however, they are turned off, the potential for unacceptable room contamination to occur should be considered.

G.5 Temporary filters

The installation of temporary filters should be considered to protect the air cleanliness of air-handling systems during construction and commissioning.

G.6 Packaging and transportation

High-efficiency air filters should be packaged in a manner that adequately protects the element from mechanical damage during handling and transportation from the supplier. The filters should be inspected and be free from damage prior to fitting into the installation.

G.7 Fitting

The fitting of high-efficiency filters should be delayed until they are required for commissioning purposes. Whilst awaiting fitting, filters should be stored in accordance with the supplier's instructions. Immediately prior to fitting, the air ducting system should be visibly clean and free from contamination. The filters should be fitted in accordance with the manufacturer's instructions.

G.8 Testing

All air filtration equipment installed in an installation should allow for leak-testing of the final filters and integrity-testing of the seals between filter and mounting arrangements. Consideration should be given to the materials used for such testing to ensure that materials themselves do not become contaminants or cause contamination.

Annex H
(informative)

Additional specification of requirements to be agreed upon between purchaser/user and designer/supplier

H.1 General

This annex is intended to assist the purchaser/user and designer/supplier to communicate and agree on additional requirements. It is intended that the checklist be used to define known requirements and identify aspects where further development is required.

H.2 Checklists

Checklists are given in the form of tables.

Table H.1 suggests a check for process requirements which affect the installation.

Table H.2 suggests a check for contaminants which detrimentally affect the process.

Table H.3 suggests a check for all pieces of equipment to be utilized in the process.

Table H.4 suggests a check for all external factors affecting the process.

Table H.5 suggests a check for environmental requirements affecting the process.

Table H.6 suggests a check to identify requirements for safe operation.

Table H.7 suggests a check to evaluate the requirements for systems redundancy (standby/backup).

Table H.8 suggests a check for the scope of equipment maintenance required.

Table H.9 suggests a check for miscellaneous requirements not previously defined that affect design, construction, operation and maintenance.

Tables H.10, H.11 and H.12 suggest checks for factors affecting future developments, cost requirements and scheduling, respectively.

Table H.1 — Process requirements

Number	Item	Description	Specified value	Achieved performance
1	Direct processes	Those which directly affect the end product or service.		
2	Indirect processes	Those which support or indirectly affect the end product or service.		

Table H.2 — Process contaminants

Number	Item	Description	Specified value	Achieved performance
1	**Matter as contaminant**	Non-viable or viable matter		
1.1	**Particulate**	Particles of different shape		
1.1.1	Class	In accordance with ISO 14644-1		
1.1.2	Size(s)	Particle size(s), M- and U-Descriptors (see annex E in ISO 14644-1:1999)/Basic, ultrafine, macroparticles and fibres		
1.1.3	Recovery time			
1.2	**Chemical**	Molecular, ionic, gaseous, condensable, metallic		
1.2.1	Amount	Quantity of chemical contamination/weight, layer(s), concentration		
1.2.2	Class	In accordance with ISO 14644-1 or other standard		
1.2.3	Recovery time			
1.3	**Biological**	Viable, aerobic or non-viable pathogenic organisms/organisms capable of reproducing		
1.3.1	General type	Bacteria, fungi, other		
1.3.2	Contamination type	Aggressive to surfaces, resistant to disinfection, pathogenicity		
1.3.3	Propagation	Duration from upset to steady state		
2	**Energy as contaminant**	Energy sources which interfere		
2.1	**Vibration**	Extent of motion		
2.1.1	Amplitude	Greatest displacement		
2.1.2	Frequency	Rate of motion		
2.2	**Magnetic**	Electromagnetic fields		
2.2.1	Field strength			
2.3	**Radio frequency**			
2.3.1	Field strength			

Table H.3 — Process equipment specification

Number	Item	Description	Specified value	Achieved performance
1	**Input utilities**	Matter and energy required to be delivered to each process equipment		
1.1	**Solids — Supply requirements**	List equipment solids to be utilized in the process		
1.1.1	Solids supply purities/ Concentrations	List, for each piece of equipment, for purities/concentrations required for all solids to be utilized in the process		
1.1.2	Solids supply quantities	List, for each piece of equipment, the quantities of all solids to be utilized in the process, including the maximum, minimum, and nominal rates of introduction and utilization		
1.2	**Gases — Supply requirements**	List, for each piece of equipment, all gases to be utilized in the process		
1.2.1	Gases supply purities	List, for each piece of equipment, the purities required for all gases to be utilized in the process		
1.2.2	Gases supply quantities	List, for each piece of equipment, the quantities of all gases to be utilized in the process, including the maximum, minimum, and nominal rates of introduction and utilization		
1.2.3	Pressures	List, for each piece of equipment, the pressures of all gases to be utilized in the process, including the maximum, minimum, and nominal rates of introduction and utilization		
1.3	**Liquids — Supply requirements**	List, for each piece of equipment, all liquids to be utilized in the process		
1.3.1	Liquids supply purities/ Concentrations	List, for each piece of equipment, the purities/concentrations required for all liquids to be utilized in the process		
1.3.2	Liquids supply quantities	List, for each piece of equipment, the quantities required for all liquids to be utilized in the process, including the maximum, minimum, and nominal rates of introduction and utilization		

Number	Item	Description	Specified value	Achieved performance
1.3.3	Liquids supply pressures	List, for each piece of equipment, the pressures for all liquids to be utilized in the process, including the maximum, minimum, and nominal rates of introduction and utilization		
1.4	**Electric power requirements**	List, for each piece of equipment, the electric power requirements		
1.4.1	Voltage			
1.4.2	Phase			
1.4.3	Frequency			
1.4.4	Load			
1.4.5	Allowable electrical power fluctuation requirements	List, for each piece of equipment, the maximum allowable fluctuation in electrical service that can be accepted without electrical power filtration		
2	**Output utilities**			
2.1	**Solid waste requirements**	List, for each piece of equipment, all solids to be rejected in the process		
2.1.1	Solids waste purities/ Concentrations	List, for each piece of equipment, the purities/concentrations of all solids to be rejected in the process		
2.1.2	Solids waste quantities	List, for each piece of equipment, the quantities of all solids to be rejected in the process, including the maximum, minimum, and nominal rates of rejection		
2.2	**Exhaust flow requirements**	List, for each piece of equipment, all types of exhaust to be utilized in the process		
2.2.1	Exhaust flow characteristics	List, for each piece of equipment, the types of exhaust flows (e.g. acid, solvent, heat, general, etc.) to be utilized in the process and their respective concentrations, and temperatures		
2.2.2	Exhaust flow quantities	List, for each piece of equipment, the quantities of all exhaust flows to be utilized in the process, including the maximum, minimum, and nominal rates of introduction and utilization		

Number	Item	Description	Specified value	Achieved performance
2.2.3	Exhaust flow pressures	List, for each piece of equipment, the pressures of all exhaust flows to be utilized in the process, including the maximum, minimum, and nominal rates of introduction and utilization		
2.3	**Liquid waste requirements**	List, for each piece of equipment, all liquids to be rejected in the process		
2.3.1	Liquid waste quantities	List, for each piece of equipment, the quantities of all liquids to be rejected in the process, including the maximum, minimum, and nominal rates of introduction and utilization		
3	**Environmental parameters**	To allow intended use of the process equipment		
3.1	**Temperature requirements**	List, for each piece of equipment, the maximum, minimum, and optimum temperature requirement, both internal and external to the equipment. Further list by equipment component separately, as required.		
3.1.1	Rate of temperature rise	List, for each piece of equipment, the maximum allowable rate of temperature rise		
3.1.2	Rate of temperature fall	List, for each piece of equipment, the maximum allowable rate of temperature fall		
3.2	**Humidity requirements**	List, for each piece of equipment, the maximum, minimum, and optimum humidity requirement, both internal and external to the equipment components as required separately		
3.2.1	Rate of humidity rise	List, for each piece of equipment, the maximum allowable rate of humidity rise		
3.2.2	Rate of humidity fall	List, for each piece of equipment, the maximum allowable rate of humidity fall		
3.3	**Vibration requirements/ Limitations**	List, for each piece of equipment, the maximum, minimum, and nominal vibration energy level		
3.4	**Physical barrier applied**	Are they required?		

Number	Item	Description	Specified value	Achieved performance
4	**Physical attributes**	Equipment dimensions and mass		
5	**Installation considerations**	How to install		
6	**Operational considerations**	How to operate		
7	**Maintenance considerations**	How to maintain		
8	**Pre-process**	Status of incoming product or starting materials		
9	**Post-process**	Description of subsequent manufacturing steps		
10	**Process throughput**	The amount of product passing through the equipment over time		
11	**Communication considerations**	Describe		
12	**Ergonomic considerations**	Describe		

Table H.4 — External factors

Number	Item	Description	Specified value	Achieved performance
1	**Regulatory requirements**	List all regulatory factors affecting site selection and operations, including local zoning laws and ordinances, local tax structures, and permitting requirements		
2	**Utility resources and factors**	List utility resources, including availability, quality, and quantities		
2.1	Site water supply	List the characteristics of local ground or municipal water supply, including toxicity, turbidity, etc.		
2.2	Site air quality	List existing site air quality characteristics		
2.3	Site electrical power factors	List the local electrical power supply characteristics, i.e. capacity, voltage, number of phases, frequency, and intensity and frequency of fluctuations, etc.		
2.4	Site waste systems factors	List the local waste system characteristics		

3	**Site vibration characteristics**	Evaluate the ambient site vibration level and its variations. Evaluate for potential impacts on planned processes and facilities		
4	**Proximity factors**	List all proximate and adjacent site structures, processes, pollutants, etc. Evaluate for potential impacts on planned processes, facilities, and personnel		
5	**Site geotechnical factors**	List all geotechnical factors, i.e. soils toxicity, soils expansion, characteristics, etc. Evaluate affect on planned installation		
6	**Security and access factors**	List all security and accessibility factors. Evaluate for affect on installation.		

Table H.5 — Environmental requirements

Number	Item	Description	Specified value	Achieved performance
1	**Ambient requirements**	Consider for process, equipment, and personnel requirements. List initially by cleanliness hierarchy. List each process area by cleanliness classification only if the design process is substantially developed.		
1.1	Cleanliness	Required cleanliness classification		
1.2	Air pattern type	List the cleanroom air pattern type, i.e. unidirectional, non-unidirectional, or mixed		
1.3	Airflow direction	List the cleanroom airflow direction, i.e. vertical or horizontal		
1.4	Air velocity	List the cleanroom air velocity within the process area		
1.5	Air circulation system and configuration	Evaluate the cleanroom air circulation system configuration. Consider process, regulatory, personnel and budgetary factors		
1.6	Dry bulb temperature	Evaluate the cleanroom dry bulb temperature requirement, including the maximum, minimum and nominal value		
1.6.1	Rate of dry bulb temperature rise	List the cleanroom maximum allowable rate of dry bulb temperature rise		

Number	Item	Description	Specified value	Achieved performance
1.6.2	Rate of dry bulb temperature fall	List the cleanroom maximum allowable rate of dry bulb temperature fall		
1.7	Humidity	Evaluate the cleanroom humidity requirement, including the maximum, minimum, and nominal value		
1.7.1	Rate of humidity rise	List the cleanroom maximum allowable rate of humidity rise		
1.7.2	Rate of humidity fall	List the cleanroom maximum allowable rate of humidity fall		
1.8	Pressurization	List the cleanroom pressure		
1.8.1	Pressurization differential	List the cleanroom pressurization differential from zone of higher space pressure to adjacent zone of lesser pressure		
1.8.2	Pressurization rate of change	List the cleanroom maximum allowable rate of change in space pressure		
2	**Sound pressure level (noise)**	List the cleanroom maximum allowable and nominal sound pressure levels		
3	**Vibration**	List the cleanroom maximum allowable and nominal vibration energy level		
4	**Lighting**	List the minimum and nominal cleanroom lighting requirements, and any wavelength restrictions		
5	**Physical geometry**	List the dimension/size requirements		
5.1	Ceiling-to-floor height	List the cleanroom ceiling-to-floor height requirement		
5.2	Floor area requirement	List the cleanroom floor area requirement, i.e. length and breadth		
5.3	Floor loading	Maximum mass loading		
6	**Ionization**	Charge balance (air)		

Table H.6 — Safety requirements

Number	Item	Description	Specified value	Achieved performance
1	Cleanroom life-safety requirements	Identify all safety codes and regulations that affect the installation		
2	Separation of air circulation zones	Evaluate specific requirements for individual zone control and segregation		
3	Storage and transport of toxic, flammable and hazardous materials	Evaluate specific process and overall storage requirements		
4	Exiting requirements	Evaluate maximum exit distance requirements		
5	Physical requirements	Evaluate requirements for fire resistive materials and assemblies		
6	Purge system	Is one required?		
6.1	Flowrate	At what rate?		

Table H.7 — Standby/backup requirements

Number	Item	Description	Specified value	Achieved performance
1	System duplication	100 % replacement capability		
2	System oversizing	More available than required		
3	Largest component backup	Replace 100 % of single		
4	Alternative source	Switch over to alternative		
5	Failure detection and reporting			
6	Change-over methodology	Manual or automatic		

Table H.8 — Operations and maintenance factors

Number	Item	Description	Specified value	Achieved performance
1	MTBF	Mean time between failures		
2	MTTR	Mean time to repair		
3	Maximum time to repair	How long to fix?		
4	Spare parts availability	How many, what type?		

Table H.9 — Personnel factors affecting people and productivity

Number	Item	Description	Specified value	Achieved performance
1	Personnel and materials flow requirements	Evaluate product and process flow requirements and personnel flow requirements. Evaluate distances between individual processes and their functional interdependencies. Evaluate personnel communications and access needs.		
1.1	Airlocks	Required?		
1.2	Gowning requirements	What type of gown(s)		
2	Operating frequency	List the operating frequency of the cleanroom, i.e. continuous versus intermittent. If intermittent, specify frequency of operation, e.g. 5 days per week, 8 h per day		
3	Ergonomics	Any requirements		
4	Aesthetics	Any requirements		

Table H.10 — Future developments

Number	Item	Description	Specified value	Achieved performance
1	Future	Planning to consider now?		
2	Flexibility	Planning to consider now?		

Table H.11 — Cost requirements

Number	Item	Description	Specified value	Achieved performance
1	Capital cost	First cost		
2	Operating cost			
2.1	Energy use	Identify ways to reduce operating costs		
2.2	Maintenance costs			
3	Life cycle cost	Owning cost		

Table H.12 — Schedule

Number	Item	Description	Specified value	Achieved performance
1	Task definition	Project tasks shall be agreed between the user and supplier		
2	Identify milestones	Identify or define key project milestones and the acceptance criteria		

H.3 Specification checklist of basic requirements for cleanroom projects

Purpose: The purpose of this form is to help the user and supplier of the cleanroom project to document the essential and non-essential aspects of the cleanroom project. This form should be used in conjunction with the normative and informative clauses of this part of ISO 14644.

Project Name: _____ Project Location: _____

Customer Name: _____ Supplier Name: _____

Customer Contact: _____ Supplier Contact: _____

Customer Phone No. _____ Supplier Phone No. _____

Date: _____

H.4 Relation to clause 4

Table H.13 — Relation to clause 4

Clause 4 reference	Description of requirement	Response, requirement, specification
4.2	What is the number of the International Standard being referenced?	
4.2	What is the date of publication of this International Standard?	
4.4	What is the general purpose for which the controlled space is to be used?	
4.4	What are the operations to be carried out in the cleanroom?	
4.4	Are there any constraints imposed by the operating criteria (see examples in annexes A, B and D)?	
4.5	What are the required classes or demands for cleanliness in accordance with the relevant parts of this International Standard (ISO 14664-1, ISO 14698-1, ISO 14698-2, ISO 14698-3) (see examples in annex F)?	
4.6	What environmental parameters will be measured for validation purposes? What are the allowable variations, measurement method(s), and calibration method(s) (ISO 14644-2 and ISO 14644-3) (see examples in annex F)?	
4.7	Describe the contamination control concept to be used to achieve the required cleanliness level (including operating and performance criteria) (see examples in annex A for description of control concepts).	
4.9	What is the material flow through the cleanroom (see examples in annex D)?	
4.10	What are the occupancy state(s) under which the required conditions shall be achieved and maintained, including variations with time, and the methods of control of occupants, including e.g. gowning, sanitation techniques, personnel flow and access control to all clean areas (see examples in annex C)?	
4.11	Provide layout and configuration drawings of the installation (see examples in annex D).	
4.12	Provide all critical dimensions and mass restrictions, including those related to available space (see examples in annex D).	
4.13/4.14	The process and product equipment to be installed in the cleanrooms or clean zones, including usage, method of gaining access for construction and maintenance, emissions, size and mass, and utility requirements (see examples in annexes B, D, E, G and H).	

Clause 4 reference	Description of requirement	Response, requirement, specification
4.15	The maintenance requirements of the system components creating the cleanroom or clean zone shall be supplied in a timely manner (see examples in annexes D and E).	
4.16	Provide the definition of all responsibilities for statement of criteria, basis of design, detailed design, construction, testing, commissioning and qualification (including the performance and witnessing) of tests (see examples in annexes E and G).	
4.17	Identify all external environmental influences, such as chemical and particle contamination, noise and vibration (see examples in annex H).	

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EXHIBITS 3-15

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EXHIBIT 16

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE NEW ENGLAND COMPOUNDING PHARMACY, INC. PRODUCTS LIABILITY LITIGATION	MDL No. 2419 Dkt. No. 1:13-md-2419 (RWZ)
THIS DOCUMENT RELATES TO: All Actions	

DECLARATION OF DR. PHILIP J. AUSTIN, PH.D.

1. At the request of the Plaintiffs' Steering Committee ("PSC") in MDL 2419, In Re New England Compounding Pharmacy, Inc. Products Liability Litigation, 13-md-2419-RWZ (D. Mass.), I have prepared the following expert declaration in connection with the cleanrooms built by Liberty Industries, Inc. ("Liberty") at and for use by the New England Compounding Center ("NECC"), in Framingham, Massachusetts. After reviewing documents and undertaking a physical inspection of the cleanrooms at NECC, I have now been requested to provide this declaration concerning the design, construction, and commission of the cleanrooms and what, if any, effect this had on the contamination of drugs compounded within the cleanrooms.

I. PROFESSIONAL BACKGROUND

I received a Bachelor of Science (1988), Master of Science (1990), and Doctor of Philosophy (1994) in Aerospace Engineering from the University of Michigan, Ann Arbor. Upon completion of my doctorate, I accepted a National Research Council postdoctoral appointment at the National Institute of Standards and Technology in Gaithersburg, Maryland. In 1996, I returned to Michigan to serve as the Director of Research for Acorn Industries, providing expert services related to cleanrooms, cleaning, and contamination control. As Director of Research for the past 18 years, I have been responsible for the majority of engineering activities which include cleaning process development, design of cleanroom

facilities and custom cleaning equipment, technical sales, and consulting services. I have worked with Acorn Industries and with hundreds of customers in the pharmaceutical and other cleanroom-related industries as an expert resource defining cleanliness requirements, troubleshooting contamination issues, developing cleaning processes, designing cleanrooms, training cleanroom personnel, and qualifying cleanrooms and cleanroom construction materials for use. A copy of my curriculum vitae is attached hereto.

II. COMPENSATION

2. I am being compensated for my work in this case at $200.00 per hour. No part of my compensation due or received is contingent upon the outcome of this litigation.

III. MATERIALS REVIEWED

3. In preparation of this declaration, I have considered the observations made by Dr. Philip R. Austin and me during the three day inspection of NECC in December 2012. I also relied upon information, including photographs and test results taken and reported by Thomas Irmiter of Forensic Building Science, the chief environmental expert and investigator designated by plaintiffs and their counsel to coordinate the inspection of NECC by various professionals and experts in December 2012. I have also reviewed Liberty's motion for summary judgment and exhibits.

IV. SUMMARY OF OPINIONS

4. It is my opinion that, to a reasonable degree of scientific certainty, Cleanroom 1, designed and constructed by Liberty Industries, was improperly designed and installed to ensure its intended use for the compounding of sterile injectable drugs. As the primary contractor responsible for the finished cleanroom, Liberty Industries was responsible for ensuring that the cleanroom was properly constructed, in all aspects, to be able to provide the required cleanliness environment for compounding sterile injectable drugs.

5. Based on the evidence currently available to me which includes my observations of defects in the ceiling of the cleanroom, the size and composition of the debris observed in the area of the defects, and my understanding of the likely operations performed in the cleanroom in the area of the defects, it is my opinion, to a reasonable degree of scientific certainty, that Liberty's failure to design and construct Cleanroom 1 was a proximate cause of the fungal contamination in NECC's cleanroom.

V. TECHNICAL BACKGROUND INFORMATION ON CLEANROOMS AND CONTAMINANTS

6. A cleanroom is an environmentally controlled production space that is specifically designed to control various forms of contamination within the space. In this context, the term "contamination" refers to any type of substance that would be detrimental to the products or processes being performed in the cleanroom; however, cleanrooms are most often designed for the purpose of controlling various forms of particulate contamination.

A. Types of Particulate Contamination

7. Particulate contamination can be composed of living or non-living material, or a combination of both. Typical living particles are bacteria, viruses, mold, and fungi. These types of living particles are often referred to as viable particles, referring to their ability to reproduce. Non-living particles can be made of anything that can be divided into small pieces through natural processes such as abrasion or erosion, or deliberate application of force to the material. Because these particles do not reproduce, they are often referred to as non-viable particles in a context where viable particles are of critical concern.

8. In a typical production environment, the most common non-living particles are hair, plant material, dead skin cells, sand, dirt, clothing particles, animal fur, animal dander, insect parts, packaging materials, plastic particles, glass particles, and metal particles. Such non-

living particles are present in a large range of sizes, from particles smaller than 1 millionth of a meter (micrometer) that are only visible under a microscope, to particles that are several millimeters long. Living particles typically have a much more narrow range of sizes that are less than a micrometer to only a few dozen micrometers, unless the living particles attach to each other or to non-living particles in groups.

9. Particulate contamination is usually thought of as solid particles such as dust, but it can also take the form of liquid droplets. These liquid droplets can in turn be carriers of small solid particles, particularly living particles.

10. Particulate contamination is pervasive in the air that we breathe and on the surface of every object that we encounter. While most of this contamination is largely invisible to us in our everyday activities, we become acutely aware of it when we see a dusty surface or notice the collection of particles floating in the air that are illuminated by a beam of sunlight in a dimly lit room. What we see in these instances are only the largest of the particles, which are visible, and only represent a small fraction of the number of particles that are actually present. The air that we breathe every day typically contains more than 1,000,000 particles larger than 0.5 microns per every cubic foot of air volume. In a production environment where such contaminants pose a risk to the product being manufactured or serviced, these contaminants must be eliminated or significantly reduced.

B. How Cleanrooms Control Particulate Contamination

11. Cleanrooms are designed to control the presence and generation of particulate contamination in a designated area. A cleanroom is an enclosed space which can be made up of one room or a series of connected rooms. The airborne contaminants in a cleanroom are controlled through the use of a special air filtration system that is designed to remove the particulate laden air from the room and replace it with filtered air which has a significantly

smaller concentration of particles. A typical cleanroom makes use of HEPA filters which are designed to remove 99.99% of all particles that are 0.5 micrometers and larger in the air that is passed through the filter. The size of the room, the number of HEPA filters, and the airflow pattern within the room are the primary factors which determine the effectiveness of the air filtration system in reducing the number of airborne contaminants within the room.

12. The contaminants in a cleanroom are also controlled by the design of the room and the materials used in the construction of the room. The cleanroom should be constructed of solid, non-porous materials that do not shed and are resistant to abrasion. A well designed cleanroom should be completely enclosed, with all surfaces, joints, ductwork, piping, tubes, and utility access openings sealed to prevent the unwanted entry of contaminants into the room. Any openings in the cleanroom provide a path for particles to enter into it via airflow into the room or gravitational settling. In particular, ceilings and wall surfaces above work surfaces within the cleanroom should be well sealed to prevent contaminants from entering via gravitational action. If such openings in a cleanroom are present, contaminants may "rain" down into the cleanroom.

13. The airborne contaminants in the cleanroom are usually further controlled through the use of air pressure which prevents contaminated air from entering into the cleanroom. In this case, the filtration system is designed to maintain the cleanroom at a small positive pressure relative to its exterior environment. Because air moves from an area of high pressure to an area of lower pressure, the higher pressure in the cleanroom results in the flow of clean air through any imperfections and gaps in the cleanroom enclosure. This flow of clean air through such gaps inhibits the flow of contaminated air into the cleanroom through these gaps.

14. Another factor which has a significant effect on the cleanliness within a cleanroom is the nature of operations that are performed within the cleanroom. Manufacturing

processes and equipment that operate within the cleanroom can generate significant amounts of contaminants which must be removed from the room in order to protect the cleanliness of operations being performed within the cleanroom. Also, personnel activity within the cleanroom can also have an impact on the cleanliness of the cleanroom, as human activity can generate large quantities of both living and non-living particles. A cleanroom that is properly designed should account for the generation of these contaminants within the room and provide for their efficient removal from the room.

C. Types and Classifications of Cleanrooms

15. Cleanrooms are often classified by the type of work that is to be performed in the cleanroom or the types of contaminants that are of primary concern in the cleanroom. Cleanrooms that are designed to specifically control biological contaminants (living particles) are typically referred to as bio-cleanrooms or aseptic cleanrooms. Such cleanrooms are used in the manufacture of certain pharmaceuticals and medical devices, and to provide services that require the absence of living particles. For cleanrooms in which there is no special requirement to control biological contaminants, there is no special designation. Such cleanrooms are used in the manufacture of automotive parts, electronics, semiconductors, aerospace parts, and other items that require an environment that is free from particulate contamination. For these types of cleanrooms, there is generally little concern whether the particles in the room are living or non-living.

16. Cleanrooms are also classified by the design of the airflow pattern within the room: turbulent flow or laminar flow. Cleanrooms can have a turbulent airflow design in which the HEPA filtered air is mixed with the “dirty” air in the cleanroom to gradually reduce the concentration of airborne particles present within the cleanroom by dilution. In such cleanrooms, the HEPA filters are typically dispersed in the ceiling of the cleanroom, covering an

area of the ceiling that is proportional to the desired level of air cleanliness within the cleanroom. The air from these filters is discharged into the cleanroom and mixes with the air inside of the cleanroom. The placement of the filters is typically designed to maximize the efficiency of the mixing process. As the filtered air is mixed with the air within the cleanroom, the concentration of particles in the air within the cleanroom is decreased by a dilution effect. The mixed air is then drawn out of the room through vents which recirculate a portion of the air through the filtration system. The manner in which a turbulent cleanroom reduces the concentration of airborne particles is similar to an air conditioning system in which cold air is introduced into a room, mixes with the warmer air in the room, and thereby lowers the temperature of the air in the room.

17. Cleanrooms can also have a more efficient airflow design, known as laminar airflow, in which the HEPA filtered air completely displaces the "dirty" air in the cleanroom. This type of cleanroom airflow was invented in 1962 to improve the capability of cleanrooms to provide lower airborne particulate levels. For this type of cleanroom, the HEPA filters cover the entire ceiling or one entire wall of the cleanroom. If the entire ceiling of the room is covered with HEPA filters, the cleanroom is designated as a vertical laminar flow cleanroom. If an entire wall of the room is covered with HEPA filters, the cleanroom is designated as a horizontal laminar flow cleanroom. For the vertical flow cleanroom design, the air flows from the ceiling HEPA filters directly down to the perforated floor of the cleanroom. The floor of the cleanroom sits above a return air plenum in which the air from the cleanroom is collected and recirculated through the filtration system. For the horizontal cleanroom design, the wall of the cleanroom that is opposite the wall of HEPA filters sits in front of a return air plenum in which the air from the cleanroom is collected and recirculated through the filtration system.

18. In the laminar flow cleanroom design, as the air is discharged from the HEPA filters, it does not mix with the air inside of the cleanroom; instead, the air from the filters "pushes" the "dirty" air through the cleanroom to the return air plenum, completely displacing the air in the cleanroom. In order for this type of cleanroom to function properly, the air velocity must be maintained at a relatively low velocity in the range of 100 feet per minute. This ensures that the body of air from the filters remains together as it moves through the cleanroom environment. The laminar flow cleanroom can be thought of as a low speed wind tunnel in which the air being supplied to the wind tunnel is HEPA filtered.

19. From an airborne cleanliness standpoint, the laminar flow cleanroom design is capable of producing a much cleaner environment because it is constantly removing all particles in the airstream by pushing them through the room to the return air plenum. The air inside of the cleanroom is continuously being completely replaced with HEPA filtered air; thus, any particles which may be generated inside of the cleanroom are quickly swept out of the cleanroom. By contrast, the turbulent airflow design will allow some particles to persist for a substantial amount of time in the air because the turbulent flow design relies on a dilution principle. In such a cleanroom, pockets of dirty air can be present which will only slowly be diluted by the mixing process. For this reason, the laminar flow cleanroom design is the preferred design for critical applications, particularly those in which strict control of living (viable) particles is required.

D. Classification and Certification of Cleanrooms per ISO 14464-1

20. Cleanrooms are also classified by their level of cleanliness, as determined by special measurements made in accordance with standards that are used to define the level of cleanliness within the cleanroom. In this regard, the concentration of particles within the cleanroom is measured and compared to a standard (ISO 14644-1) that defines classes of cleanroom cleanliness based on the concentration of airborne particles within the room.

21. ISO 14644-1 is an international standard which establishes “classes” of cleanroom cleanliness based on the measured concentration of airborne particles within the room. The concentration of particles within the room is measured using a special instrument called an airborne particle counter. This instrument ingests samples of air from the cleanroom and passes them through a detection cell which counts and sizes the particles. The instrument then reports the concentration of particles present in the air at various particle size thresholds. This concentration can then be compared to levels established by the ISO standard that define the cleanliness class of the cleanroom based on the particle concentration.

22. The levels of cleanliness defined by ISO 14644-1 were developed in conjunction with work that led to the publication of Federal Standard 209: the first public standard to define the levels of airborne particulate cleanliness within a cleanroom. The levels of cleanliness as defined in Federal Standard 209 were intuitive in that the defined cleanliness level corresponded to the number of particles larger than 0.5 micrometers in a cubic foot air sample. For example, a cleanroom designation of Class 100 defined a cleanroom with less than 100 particles per cubic foot of air that are 0.5 micrometers and larger, while a cleanroom designation of Class 10,000 defined a cleanroom with less than 10,000 particles per cubic foot of air that are 0.5 micrometers and larger. The standard also established limits for other particle sizes for the various cleanliness classes which could be used, at the discretion of the entity certifying the cleanroom, to determine compliance with a given cleanliness classification.

23. While Federal Standard 209 persisted as the public standard for defining cleanroom cleanliness for over 30 years, it was eventually replaced by ISO 14644-1 in 1999. ISO 14644-1 is a standard that was issued by the ISO (International Standards Organization). As was done for other standards issued by the US government or US military, the new ISO standard

was issued to replace a standard that was controlled by the United States with a standard that could be controlled by the international community through the ISO. While some aspects of Federal Standard 209 were modified in the ISO standard to reflect progress in the technology of cleanroom design, the basis for the definition of the airborne cleanliness levels was not changed. In this regard, the ISO standard essentially converted the Federal Standard 209 cleanliness classes to metric units and changed their names accordingly. The current system of classifying cleanroom cleanliness is less intuitive but equally valid. In general, what was referred to as a Class 100 cleanroom in Federal Standard 209 is now referred to as an ISO Class 5 cleanroom in ISO 14644-1. Similarly, a Class 1,000 cleanroom is now an ISO Class 6, a Class 10,000 cleanroom is now an ISO Class 7, and a Class 100,000 cleanroom is now an ISO Class 8.

24. Despite the adoption of the ISO standard to replace Federal Standard 209, the cleanroom industry continues to use the class designations of the Federal Standard. This is done, primarily in the USA, because the designations for the Federal Standard 209 cleanliness classes are more easily understood and because of the long history of using this nomenclature to specify the cleanliness of a cleanroom environment.

25. According to the ISO standard, cleanrooms can be certified as meeting the requirements of a particular class if they meet specific criteria. The standard defines the process for determining if a cleanroom meets the specified criteria for a given cleanliness class designation by testing the airborne particle concentration within the room. The standard defines limits for the concentrations of particles of various sizes for each of 9 different cleanliness classes: ISO Class 1 through ISO Class 9. Each decrement of one cleanliness class represents an environment that is ten times cleaner; therefore, a Class 7 cleanroom is 10 times cleaner than a

Class 8 cleanroom, and a Class 6 cleanroom is 10 times cleaner than a Class 7 cleanroom and 100 times cleaner than a Class 8 cleanroom.

26. The ISO standard allows for the testing and certification of a cleanroom under three different operational states: as built, at rest, and operational. The "as built" state is defined by the condition of the cleanroom after completion of construction, but without the presence of production equipment, product, and personnel within the room at the time of testing. Testing in the "as built" state is usually designed to demonstrate the performance of a newly constructed cleanroom prior to installation of equipment into the cleanroom which could alter the performance of the cleanroom.

27. The "at rest" state is defined by the condition of the cleanroom after completion of construction and installation of all production equipment required for normal production activities to be performed within the room. Testing in the "at rest" state is performed without personnel present in the room at the time of testing, and is typically performed while production equipment is not actively moving. Passive production equipment such as refrigerators, non-moving lab instruments, and electronics may be operational during "at rest" testing with little to no effect on the test results; while active equipment such as conveyors, robotic transfer equipment, and other items that actively move while in operation can significantly affect the test results. As such, active equipment is usually kept dormant during "at rest" testing. Testing in the "at rest" state is designed to demonstrate the performance of the fully operational cleanroom without the variables of human activity and active equipment movement within the cleanroom.

28. The "operational" state is defined by the condition of the cleanroom in its fully operational condition. Testing is performed for the cleanroom during normal production activities with equipment operating as it would during normal production and with personnel

present, performing their normal production activities. Testing in the "operational" state is designed to demonstrate the performance of the cleanroom under the same conditions for which production activities will be performed. This type of testing provides the most accurate representation of the levels of contamination to which a product will be exposed, and provides the most accurate measure of how well a cleanroom has been designed to provide particulate control for the processes being performed within the cleanroom. Testing in the "operational" state allows for the identification of specific contamination issues that can affect the quality of the product being manufactured or process being performed within the cleanroom.

E. Standards Which Apply to the Construction of Cleanrooms

29. While certification of cleanrooms is typically performed according to the requirements of ISO 14644-1, this is not the only standard that governs the proper design and operation of cleanrooms. ISO 14644-1 is merely the standard which is used to certify that a cleanroom is complaint with certain required levels of airborne particulate cleanliness. Testing in accordance with ISO 14644-1 is only the last step that is typically performed to confirm that a newly constructed cleanroom is functioning properly; however, it is not the only criterion for certification of a cleanroom as being suitable for use. ISO 14644-1 does not address the proper design and construction of a cleanroom, nor does it address unacceptable forms of contamination that are not measured using standard airborne particle count testing.

30. ISO 14644-1 is only one part of a series of standards which govern the proper design and operation of cleanrooms. These ISO standards are collectively referred to under the general title of "Cleanrooms and Associated Controlled Environments". These other standards have designations 14644-2 through 14644-14. While ISO 14644-1 is used to measure levels of airborne particulate cleanliness in a cleanroom, other tests that are recommended for the commissioning of a cleanroom are listed in ISO 14644-3. Of specific interest to an entity

responsible for the design and construction of a cleanroom, ISO 14644-4 lists requirements for the design, construction, and start-up of a new cleanroom which must be followed. It should be noted that the Foreword of each section of ISO 14644, including ISO 14644-1, references the section numbers and topics of the other ISO 14644 sections.

31. ISO 14644-4 specifically addresses the design, construction, and start-up requirements for a cleanroom. It establishes a list of requirements for the cleanroom to be agreed upon between the purchaser and supplier. It also outlines the proper process for planning and design of the cleanroom. In both of these sections of the document, it specifically addresses the intended use of the cleanroom and the ability of the cleanroom to provide a sufficiently clean environment for its intended purpose. ISO 14644-4 outlines a series of activities required for installation and approval of a cleanroom. Certification according to ISO 14644-1 is only one component of the required approval process. ISO 14644-4 also establishes specific requirements for the materials of construction and design of the cleanroom. Of particular note, it requires ceiling and wall systems to be sealed, to prevent ingress of unwanted particles into the cleanroom.

32. In addition to the ISO 14644 series of standards, other standards such as ISO 14698 and USP <797> define the requirements of cleanrooms to be used for the compounding of drugs.

VI. INVESTIGATION AND INSPECTION OF NECC FACILITIES

33. In December of 2012, my father, Dr. Philip R. Austin, and I were retained as consultants with expertise in the area of cleanroom design and contamination control. We were granted access to the NECC facility, under the supervision of federal agents and lawyers representing NECC, for a three day period in December of 2012. The purpose of our

investigation was to document the conditions of the facility and attempt to identify the likely cause(s) of the contamination of vials of MPA with fungus.

34. During our investigation, we inspected the interior of the facility and parts of the exterior on a limited basis, with our primary focus on the cleanrooms used for compounding. At the start of our investigation, we did not have any information regarding where the contaminated MPA was compounded. During our investigation, our observations led us to the conclusion that the contaminated MPA was most likely compounded in the main area of the 2006 cleanroom ("Cleanroom 1"), which we later learned was designed and installed by Liberty Industries. Information obtained since that time also appears to support the conclusion that the contaminated MPA was compounded in the main area of the 2006 cleanroom. For this reason, our analysis here is focused on this cleanroom area.

35. During our inspection of the cleanroom in December of 2012, we identified several defects in the design and construction of the NECC cleanrooms. In particular, it was our conclusion that the most probable vector for the contamination was directly related to a defect in the design and construction of the main area of the 2006 cleanroom. Although we have been provided with additional information since our initial investigation, we still believe that the defects in the design and construction of the NECC cleanrooms played a key role in the contamination of the vials of MPA.

A. Design of Cleanroom 1

36. Cleanroom 1 was designed as a system of four attached cleanrooms. The main area of the cleanroom is a large ISO Class 6 cleanroom with several smaller support cleanrooms sharing a common wall with the main area of the cleanroom. The main area of the cleanroom consists of an area of approximately 2,400 square feet which was designed as an ISO Class 6 cleanroom. This cleanroom is designed as a turbulent flow cleanroom, with 76 or 77 HEPA

filters distributed across the ceiling surface, and air return plenums at various locations along the walls and central support pillar of the cleanroom. Attached to the main area of the cleanroom is a support cleanroom, called the Preparation Room, which was designed as a turbulent flow ISO Class 7 cleanroom. This area is approximately 480 square feet and was presumably designed for support activities for the main cleanroom area. Entrance to the main area of the cleanroom is through this Preparation Room. Adjacent to the Preparation Room on one side is the Personnel Anteroom and on the other side is the Freight Anteroom. The Personnel Anteroom is designed as a turbulent flow ISO Class 6 cleanroom while the Freight Anteroom is designed as a turbulent flow ISO Class 8 cleanroom. The Personnel Anteroom has an area of approximately 220 square feet and is designed as a room through which cleanroom personnel gain access to the system of cleanrooms. Cleanroom personnel enter into this room, change into special cleanroom garments that are designed to limit their emission of particles in the cleanroom, and then proceed into the Preparation Room. As needed, the personnel will move between the Preparation Room and the main area of the cleanroom depending on the activities that they are required to perform. The Freight Anteroom, which is approximately 480 square feet, serves a similar function to the Personnel Anteroom. Raw materials are brought into the Freight Anteroom and made suitable for entry into the main area of the cleanroom.

37. The cleanrooms were constructed using a modular design with wall segments that were designed to fit together to form a sealed enclosure. The ceiling was designed to be suspended from above using a ceiling tile style grid system. The grid system was designed to hold the weight of ceiling panels, light fixtures, and HEPA filter modules that formed the ceiling surface of the cleanroom enclosure. In order for the cleanroom to function properly, it was necessary that the joints between the wall panels be properly fitted together and sealed to prevent

contaminants from entering into the cleanroom. In a similar fashion, it was necessary for the ceiling panels, light fixtures, and HEPA filters to fit properly inside of the ceiling grid to prevent contaminants from entering into the cleanroom.

38. The Personnel Anteroom and Freight Anteroom were designed to operate at a slight positive pressure relative to their external environment. The Preparation Room was designed to operate at a slight positive pressure relative to the Personnel Anteroom and Freight Anteroom, and the main area of the cleanroom was designed to operate at a slight positive pressure relative to the Preparation Room.

B. Defects in the Design and Construction of Cleanroom 1

39. The available information indicates that the contaminated vials of MPA were compounded in the main area of the cleanroom. As such, the discussion of the defects in the design and construction of the 2006 cleanroom is focused on this area of the cleanroom.

40. During our inspection of the cleanroom in December of 2012, it was observed that the ceiling system of the cleanroom was improperly designed and installed. We observed gaps between some of the light fixtures and the ceiling grid. We also observed similar large gaps between some of the HEPA filters and the ceiling grid. These light fixtures and filters should rest inside of the T shaped ceiling grid elements, with their perimeter sealing against a gasket resting on the lip of the grid elements. The weight of the lights and HEPA filters, if properly installed, should provide sufficient pressure to provide a seal that prevents contaminants from entering into the cleanroom.

41. In order for the ceiling to properly function as a barrier from contaminants entering into the cleanroom, the entire perimeter of the light fixture or filter must seal against the gasket in the grid, with no gaps or holes through which particles can enter into the cleanroom below. In the case of the main cleanroom area, gaps were observed between the grid and some

of the filters and light fixtures. In particular, one filter unit was observed to have a gap larger than 1/4" wide at its widest point, running the length of the HEPA filter on two sides, between its perimeter and the ceiling grid. When viewed from above the ceiling, one could look directly down into the cleanroom below. This gap provided for direct entry of contaminants into the cleanroom through both open unrestricted airflow and gravitational settling.

42. Of particular interest was the fact that significant amounts of debris were observed adjacent to this gap on top of the HEPA filter and adjacent lights and ceiling tiles. Most significant among the types of debris discovered were pieces of rotting wood, of various shapes and sizes, in a distribution pattern which indicated that similar debris would have fallen through the open gap in the ceiling. Rotting wood is a significant source for a variety of species of mold and fungi. Of further significance is the observation that this gap was directly above an area in which it is believed that compounding of drugs was performed.

43. Based on the size and appearance of some of these gaps in the ceiling, I believe that these defects were present as a result of the initial installation of the ceiling system. There was no observed evidence to suggest that any modifications to the ceiling had been made in these areas. Furthermore, the design of the ceiling would have made it extremely difficult for any such modifications that would have resulted in the formation of these gaps to be made without a complete replacement of the ceiling. The gaps in the ceiling were systemic based on an improper alignment of the fixed grid elements which made it impossible to seal the affected grid openings with the materials (lights, filters, and ceiling panels) designed to rest inside of the openings to seal against the grid. This means that even if a HEPA filter module was later adjusted after installation of the ceiling, it would have been impossible to position the filter in the grid without the presence of a gap between the filter and the grid.

44. In addition to the defective installation of the ceiling system, it was also observed that sprinkler heads for the fire suppression system were improperly installed. Openings for the sprinkler heads were cut into the ceiling panels and the holes were not well fit to the heads. As such, gaps between the ceiling panels and the sprinkler heads were observed. As with the gaps around the light fixtures and HEPA filters, these holes in the ceiling provided an unobstructed route of entry for contaminants into the cleanroom from above.

45. It can be argued that the positive pressure design of the cleanroom should mitigate the effect of imperfections in the cleanroom design by preventing the flow of contaminated air through these unsealed openings; however, the magnitude and location of the defects that were observed neuter this argument. While positive pressure can provide resistance to the flow of contaminated air into the cleanroom, the positive pressure is only effective to the extent that the induced air flow can support the weight of any given particle. For particles of larger size or greater density, the positive pressure airflow provides insufficient force to prevent entry of these particles into the cleanroom. In the case of the defects that were observed in the main area of the cleanroom, the holes were large and provided direct access to particles from gravitational settling. The amount of air flow through these openings, even under optimal conditions, would be insufficient to resist larger particles of solid debris or liquid droplets from entering into the cleanroom. The size and types of particles that were observed resting on the exterior surfaces of the ceiling panels, filters, and light fixtures would not be prevented from entering into the cleanroom by the positive pressure effect.

46. In addition, the fact that some of these gaps were observed adjacent to the HEPA filter modules means that the positive pressure effect would have been reduced or even reversed

due to entrainment[1] of the surrounding air by the air being discharged from the HEPA filter. The same principle that is used in the design of a turbulent flow cleanroom to encourage mixing of the air is responsible for this entrainment effect. As the air flows out of the HEPA filter, the air adjacent to the filter is drawn into the air stream. This creates a circulation pattern in the area adjacent to the filter. This circulation pattern creates a slight negative pressure along the ceiling surface next to the filter, as the surrounding air is being entrained. This phenomenon is known as a Venturi effect. This slight negative pressure is harmless unless there is a gap in the ceiling next to the filter. In this case, the slight negative pressure can draw contaminated air into the cleanroom through the gap, and mix it with the clean air being discharged from the HEPA filter. This effect can be visualized by picturing how, as the water from a waterfall falls into a pool of water below; it pulls the surrounding water from the surface of the pool down with it, creating a churning mixture of the water from the waterfall and the water from the collecting pool below. Based on our observations of some of the HEPA filters, it is likely that such entrainment of contaminants was occurring in the main area of the cleanroom, drawing small amounts of contaminated air into the cleanroom through these unsealed openings in the ceiling.

47. It was observed that Cleanroom 1 was constructed in a warehouse style building that was more than 100 years old. The construction of such a cleanroom within a building of this type requires special considerations for the interaction of the cleanroom with the surrounding building environment. In particular, the roof above the cleanroom was known to be old and in poor condition, making it likely that the roof would leak and shed debris which would fall onto the cleanroom below. In a statement from Jeffrey Erickson, the Liberty Industries site manager for the construction of the NECC cleanrooms, it is noted that he observed roof repairs being

[1] Entrainment in this context describes a phenomenon by which ambient air is pulled along in the same direction as air flowing out of the HEPA filter.

made above Cleanroom 1 during its construction, indicating his awareness of the condition of the roof. For such a cleanroom installation, in which it is likely that the ceiling of the cleanroom will be exposed to higher than usual amounts of contamination, and for which the intended purpose of the cleanroom requires safeguards from such contaminants falling into the cleanroom through the ceiling, a hardcap ceiling should be installed to protect the grid style ceiling system.

48. The construction of the cleanroom within such a large warehouse space also made the cleanroom susceptible to rapid pressure fluctuations which occur within such a space as a result of external weather conditions. Wind blowing against a building of this style, size, and age can cause rapid pressure fluctuations within the building. These pressure fluctuations can exceed the pressure differential that was used to maintain the positive pressure effect between the main cleanroom and the surrounding warehouse environment. As a result, periodic pressure inversions would have likely occurred which would force contaminants through any cracks, holes, or other openings in the cleanroom ceiling and into the cleanroom below. The pressure fluctuations in the building can also create excess negative pressure in the space above the cleanroom ceiling. This can be problematic if it creates sufficient force on the ceiling panels to lift them out of the ceiling grid. This can cause a profuse entrance of contaminants into the cleanroom as the ceiling panel is either unseated or flutters within the grid. Special hold down clips are typically used to anchor the ceiling panels to the grid in order to mitigate this effect; however, documents that I reviewed indicated that NECC experienced such problems with the ceiling panels after completion of the cleanroom. For such an installation environment, in which rapid pressure fluctuations in the area above the ceiling can be expected, a hardcap ceiling should have been used to act as a barrier to isolate the ceiling from the effects of these pressure fluctuations.

C. Insufficiency of ISO 14644-1 Testing to Demonstrate Cleanroom Compliance

49. According to the documents that I reviewed, Cleanroom 1 was tested and certified by Liberty Industries at some time near its completion. It appears that the testing was to be performed in accordance with the specified ISO 14644-1 cleanliness classes in the "at rest" condition; however, the testing was actually performed prior to the "as built" condition. Although testing for compliance with ISO 14644-1 is only one requirement for successful certification of a cleanroom as ready for use, it appears that even this requirement was handled improperly. At a minimum, ISO 14644-1 requires testing of a newly constructed cleanroom in the "as built" condition, followed by later testing in the "at rest" or "operational" condition. Liberty Industries correctly identified that they would test the cleanroom in the "at rest" condition, but failed to test even in the less stringent "as built" condition, as testing was apparently performed while significant aspects of the cleanroom construction remained unfinished.

50. The fact that the certification tests showed that the cleanrooms were in compliance with ISO 14644-1 should not be used to conclude that the cleanrooms were properly constructed to meet their designed specifications. When building a cleanroom, it is imperative that other standards, such as ISO 14644-4, are followed to ensure proper operation of the cleanroom for its intended purpose. To simply use ISO 14644-1 as the sole criterion to determine whether a cleanroom is acceptable demonstrates a lack of understanding of the criteria to be used to determine whether a cleanroom is constructed and operating properly. In addition to being able to meet the requirements for airborne particulate testing per ISO 14644-1, the cleanroom must also be properly constructed. This includes the use of appropriate construction materials and the correct use and installation of these materials to prevent external contaminants from easily entering into the cleanroom.

D. Relationship between the Defects in Cleanroom 1 and the Contaminated Vials of MPA

51. As with any biological contamination event, such as that which occurred with the contaminated vials of MPA at NECC, there are a number of possible causes. Sufficient evidence exists to conclude that the fungal contamination occurred during some aspect of the compounding process at NECC. Due to the number of possible causes for the contamination during the compounding process, it is unlikely that any definitive path of fungal contamination from an originating source to its final destination in the vials will be able to be identified. At best, only after a thorough investigation process, likely contamination paths can be identified and assigned various levels of probability.

52. It has been brought to my attention by plaintiff's counsel that defense counsel for Liberty Industries has argued that if the defects in the construction of the cleanroom were responsible for the contamination of the three MPA lots, it is probable that more than three batches of drugs would have been contaminated. This argument demonstrates a lack of understanding of cleanrooms and how contamination occurs. It is precisely the fact that the contamination occurred on only a few occasions which supports the conclusion that the defects in the cleanroom ceiling were the likely source of the fungus contamination in the cleanroom. Based on the nature of the defects in the ceiling, it is likely that the contamination was intermittent and coincided with debris falling on top of the cleanroom ceiling, changes in the building air pressure, or vibrations which could move particles from on top of the ceiling through the gaps in the ceiling. The degree and magnitude of the contamination entering the cleanroom would likely have varied significantly over time, and worsened as the cleanroom aged, as more debris collected above the ceiling. As a result, one would expect the impact of the defects in the ceiling to be an intermittent effect which would likely have become more severe over time.

VII. CONCLUSIONS

53. It is my opinion, to a reasonable degree of scientific certainty, that Cleanroom 1, designed and constructed by Liberty Industries, was improperly designed and installed to ensure its intended use for the compounding of sterile injectable drugs. As the primary contractor responsible for the finished cleanroom, Liberty Industries was responsible for ensuring that the cleanroom was properly constructed, in all aspects, to be able to provide the required cleanliness environment for compounding sterile injectable drugs.

54. Based on the evidence currently available to me which includes my observations of these defects in the ceiling of the cleanroom, the size and composition of the debris observed in the area of these defects, and my understanding of the likely operations performed in the cleanroom in the area of these defects, it is my opinion, to a reasonable degree of scientific certainty, that Liberty's failure to design and construct Cleanroom 1 was a proximate cause of the fungal contamination in NECC's cleanroom.

Respectfully submitted,

Dr. Philip J. Austin, Ph.D.

DR. PHILIP J. AUSTIN, PH.D.

Dated: December 22, 2014

Curriculum Vitae
of
Philip J. Austin, Ph.D.

11844 Brookfield
Livonia, MI 48150

Summary:

Dr. Austin is an expert in the field of cleanrooms and contamination control. As the son of the original cleanroom expert and pioneer in the field of cleanroom technology, Dr. Philip R. Austin, Dr. Philip J. Austin has been working in cleanrooms and with cleanroom technology since his childhood. He literally grew up in and around cleanrooms, and his work with cleanrooms continues to the present day. As an adolescent, Dr. Austin assisted his father with various cleanroom related projects with the family owned business which designed and manufactured cleanrooms and cleanroom components, and provided custom precision cleaning services for the aerospace industry. As an engineering student at The University of Michigan, pursuing undergraduate and graduate degrees in Aerospace Engineering, Dr. Austin collaborated with his father to write and illustrate training handbooks used in training seminars on the design and operation of cleanrooms. Dr. Austin also assisted in the editing of several of his father's books on the subject of cleanrooms. Upon completion of his Ph.D. in Aerospace Engineering, Dr. Austin accepted a prestigious National Research Council postdoctoral appointment at the National Institute of Standards and Technology in Gaithersburg MD.

After completion of his postdoctoral appointment in 1996, Dr. Austin returned to Michigan to work with his father to expand the family owned business, Acorn Industries, as Director of Research. Acorn Industries provides services based on the expert knowledge of both Drs. Austin in the area of cleanrooms, cleaning, and contamination control. The company provides precision cleaning and contamination testing services performed in their cleanrooms, cleaned containers for the fluid power, medical device, and pharmaceutical industries, and consulting services for cleanroom design and operation as well as for troubleshooting of contamination issues.

As Director of Research of a small business for the past 18 years, Dr. Austin has been responsible for the majority of engineering activities which include cleaning process development, design of cleanroom facilities and custom cleaning equipment, technical sales, and consulting services for troubleshooting of contamination issues. During his tenure at Acorn Industries, Dr. Austin has worked with hundreds of customers in the pharmaceutical, medical device, and other cleanroom related industries as an expert resource to assist them with custom solutions to their unique contamination control issues. Dr. Austin has provided both formal and informal consulting services to assist clients with defining cleanliness requirements, troubleshooting contamination issues, and developing cleaning processes. Dr. Austin has also worked closely with his father in providing additional formal consulting services for cleanroom training, cleanroom design, and troubleshooting cleanroom manufacturing contamination issues.

Education:

Doctor of Philosophy, Aerospace Engineering: The University of Michigan, Ann Arbor, 1994.

Master of Science in Engineering, Aerospace Engineering: The University of Michigan, Ann Arbor, 1990.

Bachelor of Science in Engineering, Aerospace Engineering: The University of Michigan, Ann Arbor, 1988.

Engineering Experience:

Acorn Industries
Livonia, Michigan
Director of Research / Vice-President: 2010 - Present
Director of Research: 1996 – 2010

Supervised and performed engineering activities related to custom precision cleaning services, container cleaning services, and cleanroom consulting services. Acorn Industries is a small business dedicated to providing various cleanroom services related to the control and removal of contamination. Performed research to develop hundreds of cleaning processes specific to unique customer requirements for precision parts cleaning and container cleaning. Wrote and revised more than 1,000 technical procedures and SOPs for cleaning processes, testing methods, validations, and cleanroom operations. Served as primary sales contact and technical resource for new projects with advanced technical requirements. Worked directly with customers in the pharmaceutical and medical device industries to develop custom solutions for their parts cleaning and cleaned container system requirements. Provided formal and informal consulting services to clients to assist with defining cleanliness requirements, troubleshooting contamination issues, and developing cleaning processes. Worked with pharmaceutical manufacturers and compounding pharmacies to provide technical support for their filling operations and regulatory compliance. Provided quality system management support and assistance with technical and regulatory issues. Performed and supervised validations of cleaning, depyrogenation, and sterilization processes for container and closure systems for the pharmaceutical industry. Designed and supervised construction and expansion of Acorn's cleanroom facilities. Designed custom cleaning process equipment and supervised its construction and validation. Provided cleanroom training to Acorn employees and assisted with training of consulting clients. Provided technical support for cleanroom design and certification activities for consulting clients.

National Institute of Standards and Technology (NIST)
Gaithersburg, MD
NRC Postdoctoral Research Fellow: 1994 - 1996

Performed unique research in the field of fire safety and combustion of materials. Worked on independent research projects and collaborative projects with senior researchers from the government and industry.

The University of Michigan, Department of Aerospace Engineering
Ann Arbor, MI
Teaching Assistant / Supervising Teaching Assistant: 1991 - 1993

Taught the senior level Aerospace Engineering lab course. As Supervising Teaching Assistant, revised curriculum, supervised the teaching laboratory classroom, and supervised the teaching of the course by other teaching assistants.

The University of Michigan, Department of Aerospace Engineering
Ann Arbor, MI
Research Assistant: 1988 - 1991

Performed unique research in the field of combustion of small dust particles under the supervision of professors in the department of Aerospace Engineering.

National Aeronautics and Space Administration (NASA)
Lewis Research Center
Cleveland, OH
Engineer: 1985 - 1987

Worked on various engineering projects related to the design of the electrical power system for the International Space Station. Developed the experimental package for a biological experiment for the Space Shuttle and prepared it for launch. Worked with senior engineers on various heat transfer experiments.